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A Symposium: The Significance of High-Density Lipoprotein Cholesterol in the Prevention of Coronary Artery Disease

GUEST EDITO

Antonio M. Gotto, Jr., MD, DPhil Chairman, Department of Medicine Baylor College of Medicine, Chief, Internal Medicine Service The Methodist Hospital Houston, Texas Journa

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Introduction

Antonio M. Gotto, Jr., MD, DPhil

erein are presentations from a symposium that discussed the significance of high-density lipoprotein (HDL) cholesterol in the prevention of coronary artery disease. I would like to begin by offering some background information that will help put into perspective the studies that have been carried out to date.

Whereas low-density lipoprotein (LDL) cholesterol contributes to the deposition of cholesterol in the arterial wall, HDL appears to promote the removal of these deposits. This latter process, termed reverse cholesterol transport (Fig. 1), was first postulated almost 20 years ago by John Glomset at the University of Washington in Seattle. In his hypothesis, Glomset described a process by which HDL "scavenges" cholesterol from peripheral tissues, which would include the arterial wall. According to this theory, the only means by which the body can remove cholesterol is through the liver and gastrointestinal tract

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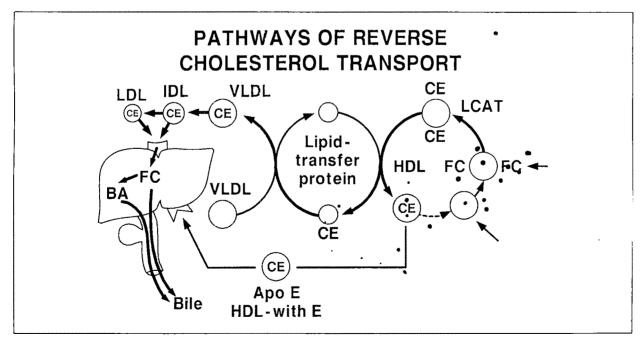


FIGURE 1. Pathways of reverse cholesterol transport. Apo E = apolipoprotein E; CETP = cholesterol ester transport; HDL = high-densi-ty lipoprotein; IDL = intermediate-density lipoprotein; LCAT = lecithin-cholesterol acyltransferase; LDL = low-density lipoprotein.

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in the form of either cholesterol or bile acid. After cholesterol is converted to cholesteryl ester, HDL either transports the cholesterol directly back to the liver or transfers the cholesteryl ester to other lipoprotein fractions (e.g., LDL), which may carry the cholesterol back to the liver for disposal (Fig. 1).

The potential for high levels of HDL cholesterol to have an antiatherosclerotic effect was first noted in the late 1940s and early 1950s by John Gofman and by Russ, Barr and Eder. These early observations were more or less overlooked until the mid 1970s, when 3 important epidemiologic studies brought HDL to the forefront of research on atherosclerosis. Our symposium participants include 3 persons who represent these studies: Norman Miller (the Tromsø Study, Norway); Peter Wilson (The Framingham Heart Study); and Basil Rifkind (the Honolulu Heart Study sponsored by the National Heart,

Lung, and Blood Institute). Until the results of these and other large clinical trials became available in the 1980s, however, there was little interest in cholesterol as a public health issue.

In this supplement, we hope to review the results of these recent trials as well as some data drawn from basic science research. We will also discuss the new guidelines for controlling cholesterol put forth by the National Cholesterol Education Program and the development of new lipid-lowering agents, including the hydroxymethylglutarvl coenzyme A reductase inhibitors. Finally, we will review the 1987 and 1988 results of the Helsinki Heart Study, which offered the first clinical evidence that increasing HDL levels and decreasing LDL levels through dietary interventions and administration of gemfibrozil can contribute significantly to reducing coronary artery disease.

High-Density Lipoprotein Cholesterol and Coronary Artery Disease: Survey of the Evidence

Basil M. Rifkind, MD

The epidemiologic evidence linking high-density lipoprotein (HDL) levels with coronary artery disease (CAD) is persuasive. Case-control studies have shown CAD patients to have lower HDL levels than control subjects. Several large-scale, observational epidemiologic studies in the United States and abroad have shown a strong independent inverse relation between HDL and CAD. Women have a lower incidence of CAD than men of the same age; this has been attributed to their higher HDL fevels. Postmenopausal women taking estrogen replacement therapy have higher HDL and lower low-density lipoprotein (LDL) levels, and a much lower incidence of CAD. Statistical analysis suggests that much of this is attributable to HDL levels.

In several clinical trials, reduced levels of total or LDL cholesterol have been accompanied by increased HDL levels. Cox proportional hazards analysis suggests that the increment in HDL levels made an independent contribution to the reduction in CAD risk. In several angiographic studies, the increase in HDL may have contributed to the decreased progression, increased stabilization and possible regression of coronary lesions.

Despite this range of impressive evidence, a number of unresolved issues have prevented the emergence of a consensus regarding the prevention of CAD by increasing HDL levels. Between-population comparisons of HDL and CAD do not match the within-population relations. Animal research on the relation between HDL, atherogenesis and CAD has been relatively scanty. Although much evidence suggests that reverse cholesterol transport partially explains the protective effect of HDL, there are still doubts as to its role. Problems with measurement of HDL have inhibited widespread recommendations for its use in prevention programs. Our ability to increase low HDL levels by hygienic means is uncertain, and there is insufficient information regarding the use of drugs for such a pur-

The recent report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, while not advocating universal screen-

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ing for HDL, did assign a risk-factor status to a low HDL level, and recommended HDL measurement in a large proportion of persons classified initially on the basis of total cholesterol levels. The results of the Helsinki Heart Study support the use of gemfibrozil in patients with high-risk LDL levels who also have borderline hypertriglyceridemia and low HDL levels.

(Am J Cardio 1990;66:3A-6A)

here are 3 well-recognized, modifiable risk factors for coronary artery disease (CAD): (1) high blood levels of total cholesterol or of its surrogate, low-density lipoprotein (LDL) cholesterol; (2) high blood pressure; and (3) cigarette smoking. The greater the level of any of these risk factors, the greater the likelihood a person will experience a coronary event (Fig. 1). Of course, if more than one these risk factors is present, the risk for CAD is correspondingly multiplied.

Both experimental and clinical research now suggests a fourth potentially modifiable risk factor: a low level of high-density lipoprotein (HDL) cholesterol in the blood. Unlike the other risk factors, however, HDL is inversely correlated with risk for CAD. The higher the HDL level, the lower the risk. Given this relation, HDL may be viewed as a potentially antiatherogenic factor. Evidence to support this protective role comes from a variety of sources. Early case-control studies indicated that patients with CAD tended to have lower levels of HDL than did matched control subjects. However, one must be cautious in interpreting such studies, since they examine a given parameter after the disease has already become manifest clinically.

The results of prospective, large-scale observational studies, such as The Framingham Study, are more reliable when trying to assess individual risk factors. In the Lipid Research Clinics Follow up Study (LRCF), in which initial observations were made in the 1970s, HDL level correlated inversely with coronary events even after adjustments were made for patient age and a variety of risk factors.

A systematic analysis of the data available from these and other studies has recently been performed by David Gordon and his colleagues. Based on an aggregate analysis of the findings in The Framingham Study, the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT), the Multiple Risk Factor Intervention Trial (MRFIT) and the LRCF, this inverse relation between level of HDL and risk for CAD was found to persist whether the population studied was male or fe-

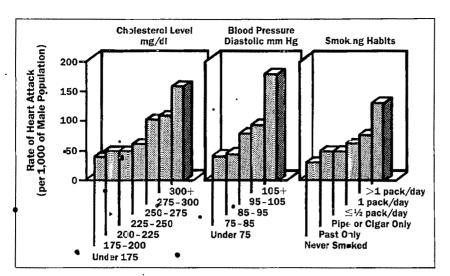


FIGURE 1. Three major coronary risk factors.

male and whether the focus was on morbid or fatal coronary events (Fig. 2). In fact, the degree of congruence among these 4 studies was striking and indicated that an increase in HDL of 1 mg/dl translates to a 2 to 3% reduction in CAD risk (i.e., a 1% increase in HDL is associated with a 1.5 to 2% reduction in CAD risk).

Additional information regarding the value of the HDL level in predicting risk has just become available from a more recent analysis of the LRCF. This study provided an opportunity to survey several thousand adults, who did not have CAD on entry into the study. At follow-up, we confirmed that the higher the LDL level, or the lower the HDL level, the greater the risk for a fatal coronary event. When we looked at a corresponding group who, at the time of entry, had evidence of CAD ranging in severity from an abnormal electrocardiogram to frank infarction, we found the same correlation be-

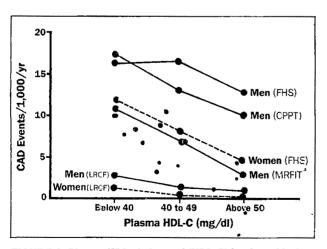


FIGURE 2. Plasma HDL cholesterol (HDL-C) levels and incidence of coronary artery disease (CAD) in four American studies. CPPT = Coronary Primary Prevention Trial, FHS = Framingham Heart Study, LRCF = Lipid Research Clinics Follow-Up Study, MRFIT = Multiple Risk Factor Intervention Trial (usual-care group only). (Reprinted from Circulation, 5 with permission of The American Heart Association, Inc.)

tween high LDL level or low HDL level and risk for a coronary event, although the absolute risk was much greater in this group than in those without CAD on entry, as would be expected. Thus, the LDL level again proved to be a strong predictor of risk, especially in those with CAD, as did the HDL level, which proved to be an important inverse predictor.

AGE AND LIFESTYLE FACTORS AFFECTING HIGH-DENSITY LIPOPROTEIN

The LRC Prevalence Study revealed that mean HDL levels in men are 45 to 55 mg/dl and are little affected by age, at least until age 55 or older. In women, however, HDL levels are 10 to 15 mg/dl higher and tend to increase with age. This may help explain why the risk for CAD is lower in women than in men until after menopause, at which point this risk begins to increase. It should be noted that we are dealing with much lower values with HDL than would be the case for total cholesterol, which may be 4 to 5 times greater. Laboratories are often unable to provide the degree of precision and accuracy that can be achieved for measurements of total cholesterol, so that repeat measurements of HDL are required for proper avaluation.

Another factor having a profound effect on HDL levels in women is the use of postmenopausal sex hormones. As is well documented, use of estrogens is associated with much higher levels of HDL compared with levels in women who do not use these hormones. On the other hand, estrogen use correlates with lower levels of LDL. Therefore, in terms of total cholesterol, the changes in these 2 component lipids with estrogen use tend to balance each other out. In the 1970s, about 30% of all postmenopausal women reported taking estrogens, and follow-up studies of this population suggest that their risk for CAD is much lower than the risk in women who did not use these hormones.

RISK FACTOR MODIFICATION AND HIGH-DENSITY LIPOPROTEIN

A number of factors have clearly emerged that appear to influence HDL levels. Many studies are exploring the

•	Men 20–69 Years (cigarettes/day)		Women 20–69 Years No Hormones (cigarettes/day)		Women 20–69 Years Taking Hormones (cigarettes/day)		•		
	0	1–19	>20	0	1-19	>20	0	1-19	>20
HDL-C (mg/di)							•		
Unadjusted	46.7	45.2	42.7	58.7	56.2	51.9	63.6	59.8	55.6
HDL-C (mg/dl)							•	•	
Adjusted for age, obesity, alcohol and exercise	46.2	43.9†	40.9 [†]	59.7	55.2 [†]	51.1 [†]	65.0	59.8 [†]	55.6
Adjusted difference 0 vs >20 (day)		5.3			8.6			9.4	

value of altering these factors to achieve a more favorable lipid profile. Principal among these factors is obesity. In almost every epidemiologic study of the relation between obesity and HDL, whether the subjects are men or women, old or young, HDL levels tend to be lower in persons with a greater degree of obesity.

Cigarette smoking, which is an independent risk factor for CAD, also has an adverse effect on HDL levels. If we look at the effect of smoking on HDL levels unadjusted for covariables such as age, obesity, alcohol intake and exercise, we find that for men and women, whether or not they take estrogens, HDL is lower by about 4 to 8 mg/dl in those who smoke heavily compared with nonsmokers. In truth, however, the effect is underestimated, since persons who smoke also often consume alcohol, and alcohol intake correlates directly with a decreased HDL level. When the values are adjusted for covariables, the change in HDL is even greater (5 to 9 mg/dl) (Table I). Although these decreases seem small, the percentage shift in HDL level is actually considerable when you consider that the denominator is only 45 to 50 mg/dl. As mentioned earlier, a 1% change in HDL could mean a 1.5 to 2% change in CAD risk.

Physical activity is believed to alter HDL level favorably based on studies using a variety of measurement techniques. We asked patients whether they considered themselves active or inactive. Although this was a rather subjective measure, it proved sensitive enough to reveal that those who were more active had higher HDL levels. Other studies have measured HDL after subjects engaged in exercise programs, and the results were similar. Many of us are familiar with the results of studies, in which marathoners or mountaineers were found to have much higher levels of HDL than did control subjects.

The potential for influencing HDL by manipulating the factors just outlined is great and, theoretically, could have a marked impact in reducing the incidence of CAD.

INCREASING HIGH-DENSITY LIPOPROTEIN LEVELS: RESULTS OF CLINICAL TRIALS

In several large-scale clinical trials designed to determine whether treatment to lower lipid levels would reduce coronary risk, the possible benefits of increasing HDL levels became apparent. In the LRC-CPPT, treatment with cholestyramine led to significant reductions in

total cholesterol and LDE and small increases in HDL, with consequent reductions in coronary risk and evidence of CAD. Upon careful statistical analysis, we found that the decrement in LDL and the increment in HDL independently accounted for these favorable effects.

More impressive results were reported from the Helsinki Heart Study, in which gemfibrozil not only reduced LDL but also increased HDL more than in the LRC-CPPT; the correlation between the increase in HDL and the reduction in CAD risk was significant (see Brown, p. 11A).

Several other studies involving drug therapy to lower cholesterol levels have also reported concomitant increases in HDL. Of particular interest is the Coronary Drug Project, in which nicotinic acid presumably increased HDL significantly. At follow-up, total and cardiovascular mortality rates were reduced even though the patients were no longer taking nicotinic acid Reductions in nonfatal and fatal coronary events were reported from the Stockholm Ischemic Heart Disease Secondary Prevention Study, in which a combination of nicotinic acid and clofibrate was used.

In the Cholesterol-Lowering Atherosclerosis Study, patients who had undergone coronary artery bypass grafting were monitored angiographically over 2 years to detect the effect of nicotinic acid and colestipol on arterial lesions. This regimen was associated with a marked increase in HDL and a profound decrease in LDL and resulted in less progression and more regression of lesions.

STRENGTHS AND WEAKNESSES IN THE EVIDENCE •

The evidence that decreasing LDL will reduce the risk for CAD is indisputable; in addition, the evidence that high levels of HDL appear to offer some protection against CAD is quite persuasive. We have a number of impressive findings: (1) CAD is more prevalent in men than in women, and women have higher HDL levels than men. (2) Postmenopausal estrogen therapy is associated with higher HDL levels, and women who use these hormones have a lower risk for CAD than do those who do not use them. (3) In general, case-control and prospective studies suggest that HDL is a powerful inverse predictor of risk. (4) A biochemical mechanism has been postulated, i.e., the so-called reverse cholesterol transport sys-

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tem, that may explain HDL's antiatherogenic effect. (5) Finally, the results of several major clinical trials strongly suggest that HDL plays a role in reducing CAD risk.

Nevertheless, some questions remain unanswered. In international comparisons, HDL level has usually been found to be a predictor of risk within populations but not between populations. Although many animal studies have been performed to determine why HDL has a prctective effect, the data are insufficient. Proposed bicchemical mechanisms remain unclear and have not been unanimously accepted. Certain genetic disorders characterized by low HDL levels predispose to CAD, whereas others do not. Because no clinical trial has shown an Increased HDL level to be the sole or predominant lipid change, other factors may be involved that contribute to the benefits reported. Finally, our ability to increase HDL levels through lifestyle modifications is variable, and information concerning the effectiveness of drugs for increasing low HDI levels is insufficient.

HIGH-DENSITY LIPOPROTEIN AND THERAPEUTIC GOALS

There has been some criticism of the National Cholesterol Education Program Panel Guidelines over the fact that they pay too little attention to HDL. In the guidelines, HDL is measured as part of the lipid profile assessment, which is performed only if the total cholesterol level is \geq 240 mg/dl, or if a patient has a total cholesterol level of 200 to 239 mg/dl plus 2 or more risk factors or known CAD. Even if increasing the HDL level does not become a primary goal of therapy, its role as a powerful predictor of CAD risk will not diminish.

As articulated by the Panel, the primary goal of hypocholesterolemic therapy is to reduce LDL levels. However, in response to the announcement of the results of the Helsinki Heart Study, a footnote was added to the Guidelines, stating that gemfibrozil might be considered a firstline agent in patients with high LDL and triglycerice levels, and low HDL levels (i.e., LDL >190 mg/dl, triglycerides >250 to 500 mg/dl and HDL <35 mg/dl). Predominantly, these are patients with type IIb hyperlipidemia, as noted in the Food and Drug Administration indications for gemfibrozil.

CONCLUSIONS

As the story of HDL continues to unfold, we hope to see some of the evidence presented amplified by additional clinical trials. Certainly, HDL level can be considered a powerful predictor of CAD risk, and the findings to date are persuasive enough to warrant further exploration. It is hoped that the information obtained will guide us in managing those persons at high risk for CAD.

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High-Density Lipoprotein, Low-Density Lipoprotein and Coronary Artery Disease

Peter W.F. Wilson, MD

Lipoprotein cholesterol data from the Framingham Heart Study show that low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol levels are important in determining risk for coronary artery disease (CAD). Increased LDL and decreased HDL cholesterol levels are associated with an increase in CAD. Such relations are independent of the usual coronary risk factors, such as cigarette use and hypertension. A 1% greater LDL value is associated with slightly more than a 2% increase in CAD over 6 years; a 1% lower HDL value is associated with a 3 to 4% increase in CAD. Even at total cholesterol levels <200 mg/dl. lower HDL levels are associated with increased myocardial infarction rates in both men and women. Death from CAD is increased when HDL levels are low, but there is no such relation between HDL level and cancer death. Triglyceride levels were associated with CAD in Framingham men and women, but the association was no longer significant in men after adjustment for HDL levels. The major determinants for greater HDL levels in Framingham participants included female sex, estrogen use, leanness, greater alcohol intake, exercise, abstinence from smoking and lack of diuretic or β -blocker use.

(Am J Cardiol 1990;66:7A-10A)

ince 1954, the Framingham group has been studying low-density lipoproteins (LDL). In the initial studies, β particles were measured (Svedborg fraction 0 to 20) and pre- β particles (fraction 20 to 400) were also determined. Using this early method, it was not possible to detect the high-density particles present at the bottom of the sediment.

If we look at the data collected over 28 years of followup, we can already see evidence of the relation between LDL and very low density lipoprotein (VLDL) levels and coronary artery disease (CAD). In 1972, lipoprotein cholesterol ractions were determined, allowing us to investigate the relation between high-density lipoprotein (HDL) cholesterol and CAD events in men and women using a sample of about 2,800 participants who attended that clinical examination. This group did not include persons younger than age 50 years, and the results represented a follow-up of only 6 years.

At 12-year follow-up of the original cohort, we examined HDL and total cholesterol by quartiles and found that the protective effect of HDL cholesterol with regard to the incidence of myocardial infarction (MI) in men was statistically significant: as HDL cholesterol decreased and total cholesterol increased, the incidence of myocardial infarction increased (Table I).^{3,4} The impact of total cholesterol is weaker as a risk factor after age 60, but it is still significant. Our report of these findings came out at about the same time the National Cholesterol Education Program Guidelines were issued, and as can be seen from the tables, even those participants with a total cholesterol level <200 mg/dl were having heart attacks. In this case, about 10 to 20% of events would have been missed if the guidelines had been applied. If a cutoff value of <35 mg/dl for HDL in men were used, about 10% of the eventual victims of MI would go undiagnosed. The same basic results were observed among the women studied (Table II), although the CAD event rates were lower, even among postmenopausal women. Therefore, with accurate HDL measurements and screening, it should be possible to adequately detect ≥90% of those at risk for

In the early 1970s, we measured triglyceride levels in addition to HDL and total cholesterol levels in the Framingham cohort. Among the men, we found a statistically significant relation between HDL and CAD events adjusted for age at 14-year follow-up; however, when triglyceride levels were factored in, they did not affect this result (Fig. 1). In contrast, for the women, both a low HDL level and a high triglyceride level were associated with risk for CAD (Fig. 2). Therefore, measurement of triglyceride levels may prove useful over and above its value in calculating LDL, at least in women.¹

From Framingham, Massachusetts.

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A SYMPOSIUM: HDL CHOLESTEROL IN CORONARY ARTERY DISEASE

TABLE I Age-Adjustec 12-Year Incidence (Rate/100) of Myocardial Infarction by Quartile of High-Density Lipoprotein Cholesterol Within Each Quartile of Total Cholesterol Among Men

		Total Cholesterol Quar	Total Cholesterol Quartile (mg/dl)				
HDL •Quartile	1st (116 to 192*)	2nd (193 tc 215)	3rd (216 to 244)	4th (245 to 376)			
1st	•	17.1 (12/71)†	17.0 (10/59)	12.9 (8/67)	14.3 (6/42)		
2nd		• 9.5 (7/71)	18.0 (11/61)	18.3 (11/59)	14.2 (12/84)		
3rd		7.0 (4/56)	12.5 (8/64)	20.2 (12/60)	19.7 (0/51)		
4th*		2.2 (1/49)	13.1 (10/76)	8.7 (6/64)	10.9 (8/73)		

Significant HDL effect in given range of total cholesterol: p <0.01.
 Values in parentheses represent the number of events/number at risk.

TABLE II Age-Adjusted 12-Year Incidence (Rate/100) of Myccardial Infarction by Quartile of High-Density Lipoprotein Cholesterol Within Each Quarti e of Total Cholesterol Among Women

	Total Cholesterol Quarti	Total Cholesterol Quartile (mg/dl)				
HDL Quartile	1st (124 to 211*)	2nd (212 to 237*)	3rd (238 to 266*)	4th (267 to 412†)		
1st	9.4 (10/104) [‡]	7.6 (7,′91)	12.6 (10/77)	13.1 (11/84)		
2nd	5.4 (5/91)	7.8 (7, '89)	5.6 (5/90)	10.7 (9/84)		
3rd	6.0 (5/84)	5.9 (7, '83)	5.3 (5/96)	8.9 (8/90)		
4th	1.3 (1/80)	0.0 (0, 485)	2.3 (2/91)	2.0 (2/99)		

Significant HDL effect in given range of total cholesterol: p <0.05.
 Significant HDL effect in given range of total cholesterol: p <0.01.
 Values in parentheses represent the number of events/number at risk.

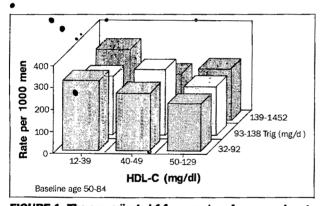
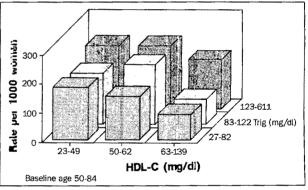


FIGURE 1. The age-adjusted 14-year rates of coronary heart disease in relation to triglyceride (Trig) and high-density lipoprotein cholesterol (HDL-C) levels for men. (Reprinted with permission from Can 1 Cardiol.1)



FFGURE 2. The age-adjusted 14-year rates of coronary heart disease in relation to triglyceride (Trig) and high-density lipoprotein cholesterol (HDL-C) levels for women. (Reprinted with permission from Can J Cardiol. 1)

Over the next few years, we should learn more about other conditions for which high lipid levels are markers, such as obesity and insulin resistance, particularly in postmenopausal women. The Framingham Study is one of the few studies to look at HDL cholesterol and mortality. It appears that there is no relation between HDL level and cancer death, but HDL cholesterol seems to be an important risk factor in coronary, cardiovascular and allcause mortality, particularly in men.5

When advising patients about steps they might take to reduce their risk for CAD, we have found it useful to summarize those factors that appear to increase and decrease HDL level (Table III). Factors that increase HDL are behavioral or hygienic factors, such as leanness, alcohol intake and exercise, as well as estrogen replacement therapy. Factors that decrease HDL level include obesity, cigarette smoking, androgens, inactivity and use of thiazide diuretics. Genetic factors may also affect HDL cholesterol, and cardiovascular medications such as α and β blockers are now being evaluated with regard to their effects on HDL and, more recently, apolipoprotein AI.6

In a study of the Framingham offspring, at 8-year follow-up we found that not only do obese persons have lower HDL levels, but a weight increase of about 5

Increased Level	Decreased Level
Leanness	Obesity
Estrogens	Androgens
Alcohol intake	Cigarette smoking
Exercise	Inactivity
	Diuretics
Alpha blockers	Beta blockers
Genetic	Genetic

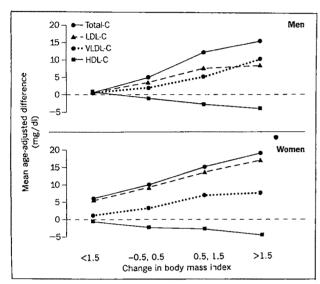


FIGURE 3. Relation of changes in lipid levels and weight in Framingham offspring (1974–1982), C = cholesterol; HDL = high-density lipoprotein; LDL = low-density lipoprotein; VLDL = very low density lipoprotein. (Reprinted with permission from Atherosclerosis.⁷)

pounds (or 1 unit according to the body mass index) is associated with a 5% decrease in HDL level, as well as increases in LDL and VLDL levels (Fig. 3).

Similarly, persons who smoke 2 packs of cigarettes per day have HDL levels of 3 to 5 mg/dl less than nonsmokers. Alcohol intake, exercise, and HDL level appear to be interrelated, as shown in a study in which subjects drank no beer at baseline and then drank 1 liter/day of beer for 3 weeks. For those who were active (in this case, joggers), HDL cholesterol changed very little during the 3-week period, whereas HDL levels in the inactive subjects increased but then decreased with abstention (Fig. 4).9

Diet is another important factor affecting HDL cholesterol. In a study performed in the mid 1970s, we compared a control group from among the Framingham offspring with a group of macrobiotic vegetarians. HDL, VLDL, LDL and total cholesterol levels were all lower in the vegetarian group (Fig. 5). ¹⁰ Based on this study, persons eating vegetarian diets should probably not be expected to have increased levels of HDL cholesterol.

Researchers are also trying to determine whether HDL subfractions (HDL₂ and HDL₃) are cardioprotective. In the earliest studies, methods of measuring these subfractions involved ultracentrifugation and were very

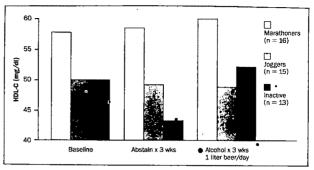


FIGURE 4. Effect of alcohol intake on high-density lipoprotein cholesterol (HDL-C) in runners and inactive men. (Reprinted with permission from JAMA.9)

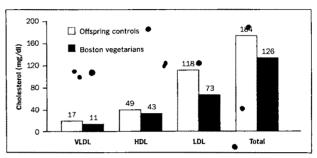


FIGURE 5. Mean plasma lipids and lipoproteins in vegetarian subjects and Framingham offspring (control group). Abbreviations as in Figure 3. Mean values are written above bars. (Reprinted with permission from *N Engl J Med.*¹⁰)

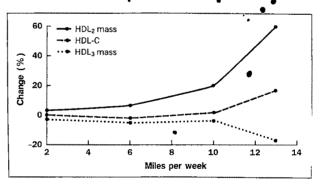


FIGURE 6. High-density lipoprotein cholesterol (HDL-C) changes observed with increased exercise. (Modified from *Metabolism.*¹¹)

expensive. Later tests have involved a process of precipitation; therefore, results may not be comparable to those obtained in the initial studies. For example, the early results suggested that HDL₂ is more cardioprotective, but recent results suggest that both HDL₂ and HDL₃ confer some protection. Figure 6 shows changes in HDL cholesterol with exercise from a study by Wood¹¹ in Stanford, California. Joggers who ran 10 miles per week for 10 months showed a 10% increase in HDL, particularly HDL₂.¹¹

In the Framingham Study, 12 exercise also appeared to have a cardioprotective effect with regard to lipid levels. Among the Framingham offspring who exercised for ≥ 1 hour each week, there was a difference of 6 to 7 mg/dl in

A SYMPOSIUM: HDL CHOLESTEROL IN CORONARY ARTERY DISEASE

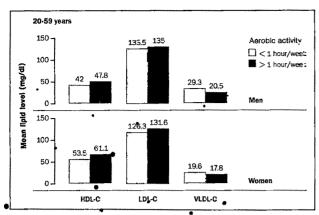


FIGURE 7. Physical activity and lipid levels as observed in Framingham offspring (1979-1983). Abbreviations as in Figure 3. (Reprinted with permission from Am J Epidemiol. 12)

the men and of 7 to 8 mg/dl in the women (Fig. 7). This translates into a level of cardioprotection of 15 to 25%.

What about the impact of estrogens taken after meropause? In postmencpausal women, the LDL level begins to increase and the HDL level begins to decrease. Estrogen therapy, at the doses given today, does seem to prevent this decrease in HDL. However, the risks and ber.efits of postmenopausal estrogens with regard to heart disease, cancer and osteoporosis are now being debated.13-17

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Clinical Trials Including an Update on the Helsinki Heart Study

W. Virgil Brown, MD

The incidence of myocardial infarction (MI), sudden death and other clinical manifestations of coronary heart disease can be reduced by lowering the blood cholesterol level. This is now well established by multiple clinical trials using a variety of interventions including diet and lipid-lowering drugs. Dietary studies in Los Angeles and in Oslo, Norway, have induced a reduction in blood cholesterol of between 10 and 15% with correlated reductions in coronary disease of 20 to 50%. Both niacin and clofibrate in separate cohorts demonstrated a significant reduction in new MI during 5 years of treatment in the Coronary Drug Project. Similar reductions in new MI occurred in the World Health Organization Study with clofibrate, However, in this trial and different from all other trials, mortality in the drug-treatment group actually increased. This finding remains unexplained.

In the more recent Lipid Research Clinics Coronary Primary Prevention Trial using the bile acidbinding resin cholestyramine, only a 9% reduction in total cholesterol resulted in a highly significant reduction in the major end points-MI and sudden death—as well as in other secondary end points, including the need for coronary artery bypass graft surgery, ischemic changes on exercise electrocardiography and new-onset angina. Recently, another primary prevention trial using gemfibrozil produced a similar reduction in total cholesterol but a much more significant increase in high-density lipoprotein cholesterol. The reduction in coronary heart disease was in excess of 34% and was strongly related to both low-density lipoprotein cholesterol reduction and high-density lipoprotein elevation.

Combination drug studies have produced larger reductions in total cholesterol. In the Stockholm Heart Study, niacin and clofibrate produced a statistically significant reduction in total mortality in patients who had had recent MI. Similarly, in men who had undergone coronary artery bypass graft surgery, the combination of niacin, colestipol and diet produced strong evidence of a reduced rate of progression of arteriosclerotic lesions as demonstrated by coronary angiography. This study, conducted at the University of Southern California, was the Cholesterol-Lowering Atherosclerosis Study. It also produced evidence of lesion regression in some patients.

From the Medlantic Research Foundation, Washington, DC. Address for reprints: W. Virgil Brown, MD, Medlantic Research Foundation, 108 Irving Street NW, Washington, DC 20010. Although these studies have been carried out primarily in middle-aged men, the older segments of these populations have appeared to do as well with regard to disease prevention as the younger members of the cohorts. We can now treat patients with high blood cholesterol levels both before and after manifestation of coronary disease with significant assurance that beneficial effects will accrue. Additional studies with newer and more powerful lipid-lowering agents are needed, as are studies in women and the elderly.

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efore reviewing some of the clinical trials designed to elucidate the role of lipids in coronary artery dis-Dease (CAD), I would like to acknowledge the extensive animal research that preceded these trials. Many different animal species, including primates, were studied in an attempt to understand the effects of cholesterol on. coronary vessels. In general, those studies showed that diets high in cholesterol and saturated fat produced high levels of cholesterol in the blood. High blood cholesterol is necessary for the development of arteriosclerosis. Conversely, when dietary cholesterol was reduced in these experiments, not only did new atherosclerotic lesions fail to appear, but existing lesions were also seen to regress. Certainly, we have relied on these animal data in developing our clinical approach to this problem and in choosing therapies for reducing blood levels of cholesterol.

WHAT CAN BE EXPECTED?

Each of the clinical trials under discussion was designed to answer a specific question or questions. Frequently, however, these trials have been criticized because they have not provided answers to all our questions, even though they may have satisfactorily fulfilled their original goals. For the most part, these trials have focused on risk for CAD and, more specifically, the incidence of myocardial infarction (MI) and sudden death. Since these events are definite, they are so-called "hard" end points. Although in many cases additional interesting observations were made and these could be used to build new hypotheses, they were not necessarily related to the original intent of the investigators. Therefore, I think we should keep these points in mind as we judge the outcomes of these trials, which involved the use of diet, drug therapy or both to reduce cholesterol levels in the blood.

Results of epidemiologic and experimental studies clearly indicated that high blood cholesterol levels were a risk factor for CAD. On this basis, clinical trials were designed to determine whether lowering blood cholesterol

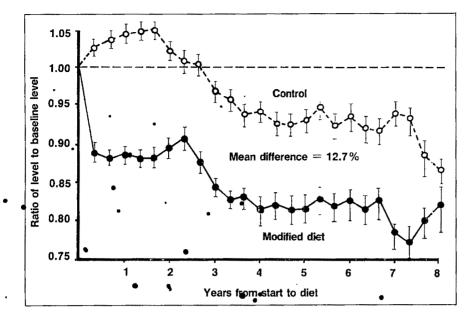


FIGURE 1 Relative change in serum cholesterol achieved in the Wadsworth Veterans Administration Study. Patients receiving a lowsaturated fat, low-cholesterol diet showed an immediate decrease in cholesterol of 12%. Values in the control group remained, on average, 12.7% higher than those in the modified diet group. (Reprinted with permission from Circulation.1)

in middle-aged persons could indeed reduce the incidence of CAD significantly. This has proved to be a difficult task. I will review a few of the earliest clinical trials to provide some perspective.

EARLY TRIALS

In the Wadsworth Veterans Administration Study, 800 veterans, the voungest of whom was 54 years of age. were randomly divided into 2 groups: 1 group continued to eat food from the hospital's usual kitchen, whereas the other group received a special diet that was lower in saturated fat and cholesterol. There was an immediate decrease in mean total cholesterol of about 13% in the group with the modified diet; over the course of 8 years, an average difference of 12.7% was maintained between the modified diet and control groups (Fig. 1).

Although the total cholesterol levels in the control group did decrease slowly as the study continued, possibly because vegetable oil began to be used instead of saturated fat in the hospital kitchen, the difference between the groups persisted simply as a result of the difference in dietary composition. At 3 years, the number of cardiovasculr end points was significantly lower for the experimental group. This study was not considered conclusive because the end points were a mix of different vascular events, many of which could not be measured using standard assessment tools and some of which were somewhat subjective, such as the occurrence of angina pectoris. In addition, some participants already had CAD; therefore, the study could also be seen as an exercise in primary as well as secondary prevention. Nevertheless, when the data were analyzed further, the researchers found that the differential was highest in the men who were below the mean age of the entire group and had higher cholesterol levels, although even among the older subjects there was a trend toward fewer events in the experimental group.

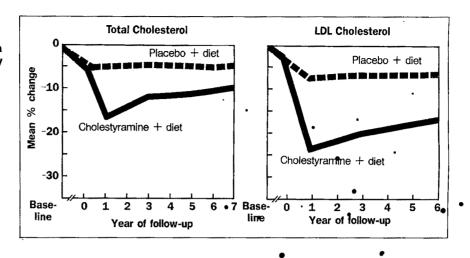
A few years later in the study by Leren² in Oslo, men who already hac CAD were given a low-cholesterol, lowfat diet with similar results. The incidence of all coronary end points was significantly reduced, although, again, the number of "hard" events (i.e., MI and death from CAD) was too small for these results to be considered conclusive.

Another dietary trial in Oslo that grew out of the Leren study was conducted by Hjermann and colleagues,3 who addressed the question of primary prevention of CAD. Participants were men whose mean total cholesterol level was approximately 325 mg/dl. They were assigned to either a treatment group or a control group, and all were instructed to undergo an annual clinical examination and report the results to their physicians. Intervention consisted of dietary therapy to lower cholesterol and a smoking cessation program, which resulted in a 12% decrease in total cholesterol levels and a 50% reduction in the smoking rate. After 90 months of monitoring, the incidence of cardiovascular events (MI and sudden death) was about 3% in the treated group and almost 6% in the control group, although the untreated patients did show a modest decrease in cholesterol during the follow-up period.

Thus, in these early studies, dietary modification was effective in decreasing the cholesterol level significantly, with a positive outcome in terms of coronary end points.

In an attempt to provide more conclusive evidence of the relation between blood cholesterol and CAD, the National Heart, Lung, and Blood Institute (NHLBI) recommended that nationwide studies be carried out in large cohorts to achieve a more significant and valid reduction in CAD risk as a result of diet and drug therapy. It was decided that men would be studied, since the incidence of CAD is higher in men than in women and therefore the study could be conducted at much lower cost.

FIGURE 2. In the Lipid Research **Clinics Coronary Primary Preven**tion Trial, decreases in total plasma cholesterol (left panel) were initially induced with dietary changes. These changes were maintained in the placebo-treated group. In the cholestyramine-treated group, an additional reduction in cholesterol averaged 9% over 7 years. This was due primarily to a decrease in low-density lipoprotein (LDL) cholesterol (right panel). LDL was 11% lower compared with the levels in the placebo-treated group over the entire study period. (Reprinted with permission from JAMA.4)



THE LIPID RESEARCH CLINICS CORONARY PRIMARY PREVENTION TRIAL

The study design chosen for the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT), described earlier by Rifkind (p. 3A), was based on the recommendations put forth by the NHLBI.⁴ Middleaged men (35 to 59 years old) with total cholesterol levels >265 mg/dl were given a modified diet and then monitored. Those who did not respond dramatically to this treatment (i.e., who maintained a level of low-density lipoprotein (LDL) >175 mg/dl) were then randomized in double-blind fashion to diet plus placebo or diet plus the bile acid-binding resin cholestyramine. Follow-up lasted 7 to 10 years.

The men selected for this study had no clinical evidence of CAD, although a positive exercise electrocardiogram was accepted as a risk factor. The primary end point was definite CAD as evidenced by sudden death or nonfatal MI, as judged by specific criteria. Other important measures were monitored as well, such as all-cause mortality, the appearance of angina (Rose questionnaire), an exercise electrocardiogram positive for ischemia and the need for coronary artery bypass grafting. The final cohort consisted of 3,806 men drawn from almost half a million candidates screened. Baseline characteristics for the 2 treatment groups were similar; mean total cholesterol 292 mg/dl; mean LDL 219 mg/dl; highdensity lipoprotein (HDL), average for men age 47; cigarette smokers 37%; blood pressure 120/78 mm Hg. This population differed from the Helsinki Heart Study, which will be discussed next, in that the mean blood pressure was significantly lower in the LRC-CPPT.

Treatment with cholestyramine led to an immediate and dramatic decrease in both total and LDL cholesterol levels (about 17 and 30%, respectively) following the initial lesser decreases that had been achieved with diet alone (Fig. 2). The group given diet plus placebo maintained average reductions of 8 or 9% in total cholesterol and 11% in LDL over the 7-year follow-up period compared with results in the placebo-treated group. The change in cholesterol values in the cholestyramine-treated group was actually less than had been predicted owing

to less than total compliance to therapy: only about 60% of the doses of drug and placebo were actually taken. Still, the difference between the 2 groups was statistically significant.

A reduction in total cholesterol of only 9% led to highly significant reductions in the primary end points, as well as in the secondary end points. In the drug-treated group, there was a 19% reduction in major cardiovascular end points (i.e., MI and death from CAD) Importantly, other CAD end points were reduced to the same degree. For example, the need for bypass surgery was reduced 20%, and the rate of angina was decreased 25%. In addition, there was a clear, proportional dose-response effect which indicated that the intervention was responsible for the change in the rate of CAD. Those with a 20% reduction in cholesterol had a 40% reduction in risk for CAD.

THE HELSINKI HEART STUDY

This more recent primary prevention trial involved a similar population of men in Helsinki, Finland.⁵ Again, the study was double-blind and placebo-controlled. Over 4,000 men were randomized to either gemfibrozil or placebo and were followed for 5 years, with clinical and laboratory examinations every 3 months. Compliance was good, and no patient was lost to follow-up. Later in this supplement (p. 24A), Manninen will bring us up to date on subsequent analyses of this trial concerning the value of HDL measurements. Here, however, I will focus on the initial study, which was designed to show a statistically significant reduction in Mland sudden death, as did the LRC-CPPT.

Although most of the baseline characteristics in these 2 studies are comparable, mean systolic and diastolic blood pressures were both about 13 mm Hg higher in the Helsinki group. In addition, total cholesterol was slightly lower and HDL slightly higher in the Helsinki group. The entry criterion was a non-HDL cholesterol level (i.e., LDL plus very low density lipoprotein cholesterol) >200 mg/dl; therefore, triglyceride levels were slighly higher in the Helsinki group.

The effect of gemfibrozil on triglyceride levels proved to be dramatic. Despite some recidivism, reductions of 30

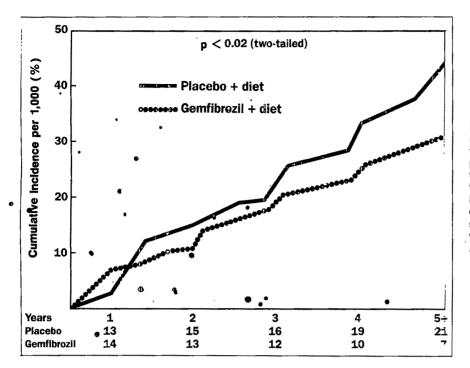


FIGURE 3. Cumulative incidence of myocardial infarction and death from coronary artery disease for placebo-treated and gemfibroziltreated groups over the 5 years of the Helsinki Heart Study (Kaplan-Meier method). The actual incidence by year of these end points is shown below the figure. (Reprinted with permission from N Engl J Med.5)

to 40% were maintained throughout the 5-year follow-up period. With regard to cholesterol, the results consisted of reductions of between 10 and 11% for both total and LDI. cholesterol. The decrease in LDL was primarily responsible for this difference. In contrast to the results achieved with cholestyramine in the LRC-CPPT, gemfibrozil produced a significant increase in HDL cholesterol, averaging 11%.

If we look at the cumulative incidence of primary cardiac end points, there was very little difference between the treatment and placebo groups for the first 3 years of the trial. However, over the next 2 years, the difference became pronounced: The rate of cardiac events was 34% less in the group treated with gemfibrozil—i.e., there were 2.5 times as many events in the group taking placebo by the end of the fifth year (Fig. 3). It is important to appreciate that the benefits of therapy may not become apparent immediately during the course of ϵ clinical trial. For this reason, long-term follow-up is extremely valuable.

Let's take a closer look at the effect on HDL in the Helsinki Heart Study. The subjects who had the lowest HDL levels at the start of the trial had the greatest increase in these levels in response to drug therapy: HDL levels <35 mg/dl increased more than 25% during the study, whereas the change was less dramatic when HDL levels were higher at the outset. Even when these values were adjusted for baseline levels, the increase was more significant in the low HDL range.

When end points were analyzed with respect to various lipoprotein disorders, gemfibrozil-treated persons with type IIa hyperlipidemia (i.e., high LDL but normal triglyceride levels) had a decrease in end points of about 24%. Among those with higher triglyceride levels the reduction was more impressive, over 40%. This may have

been due to a more dramatic rise in HDL in this group. The portion of the cohort who had the greatest benefit in terms of risk prevention were those with the lowest baseline HDL cholesterol values. The reduction in coronary events exceeded 60% in this group. In contrast, reexamination of the data from the LRC-CPPT by Gordon et al⁶ indicates that parients with normal or high HDL levels gained the most benefit from treatment with cholestyramine. This presents a series of interesting questions that remain to be explored concerning how various interventions change the rate of events.

CHOLESTEROL-LOWERING ATHEROSCLEROSIS STUDY

This study is important because it clearly showed that a person with CAD can still benefit from preventive therapy. In this trial, the investigators used a global score to assess the effect of a diet and lipid-lowering drug regimen on atherosclerotic lesions in men who had undergone coronary artery bypass grafting.7 Overall, among 160 patients who completed the study, vascular lesions in native vessels and in venous grafts, as defined angiographically, were reduced relative to those in the control group after only 2 years of combined treatment with maximal doses of colestipol and nicotinic acid. Old lesions grew less rapidly, and the number of new lesions decreased. These changes followed marked lipoprotein changes: LDL decreased 43% and HDL increased 37%. Thus, massive cholesterol reductions successfully reduced the progression of atherosclerosis in these patients with severe CAD.

CORONARY DRUG PROJECT

It has been said that there is no evidence that the lowering of cholesterol level reduces total mortality. Al-

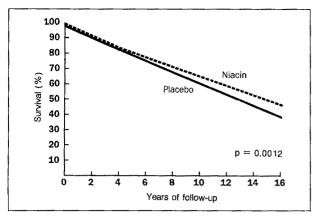


FIGURE 4. In the Coronary Drug Project (CDP), the niacintreated group showed essentially no difference compared with the placebo group in total survival over the 5-year treatment period. Subsequently, the placebo-treated group showed a more rapid decrease in survival, with a highly significant difference between the groups after 15 years. (Reprinted with permission from J Am Coll Cardiol.⁷)

though the Coronary Drug Project was not designed to evaluate this possibility, after 15 years of follow-up we now see a significant decrease in the cardiovascular mortality rate in the group that received treatment with nicotinic acid (Fig. 4). For the initial 5 years of the study, no difference in survival was observed between the treatment and placebo groups. However, at 12 and 15 years after entry into the study, the reduction in deaths due to coronary disease was great enough to affect overall mortality with a high degree of statistical significance. The improvement in total mortality must be considered observational data, since it was not addressed in the trial and did not occur during the prescribed treatment phase.

STOCKHOLM ISCHEMIC HEART DISEASE SECONDARY PREVENTION TRIAL

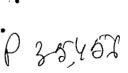
With use of a regimen similar to that in the Cholesterol-Lowering Atherosclerosis Study, a recent study from Stockholm assessed the effects of diet plus colestipol and clofibrate on subsequent events in men who had experienced MI in the preceding 4 months.⁹ Over a 5-year follow-up period, the drug-treated group showed a statistically significant decrease in total mortality, which was predominantly attributable to a reduction in cardiovascular mortality, compared with a control group treated only with a change in diet.

CONCLUSIONS ·

There is a strong body of evidence that cholesterol can be decreased by means of diet, drug treatment, or both, and that the outcome is often encouraging. Results in several clinical trials have reached statistical significance, with important clinical implications. In judging their relevance to the practice of medicine, it is useful to remember that the patients in trials do not know their cholesterol levels and thus the response cannot be used in promoting compliance. The investigator cannot judge lack of response and choose additional treatments in the compliant subjects. The benefits are judged in a relatively short time frame and the carry-over of benefits into subsequent decades of life is not measured.

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Pharmacotherapy of Disorders of Plasma Lipoprotein Metabolism

Norman E. Miller, MD, DSc

Pharmacologic intervention for altering plasma lipoproteins is aimed principally at reducing atherogenesis and thereby preventing coronary artery disease. These drugs should be prescribed only after nonpharmacologic interventions (reduction of saturated fat and cholesterol consumption, weight reduction, aerobic exercise, cessation of cigarette smoking) have failed to achieve an adequate effect.

The plasma concentration of the atherogenic low-density lipoprotein (LDL) may be reduced in hypercholesterolemic patients by increasing hepatic LDL receptor synthesis (bile acid sequestering resins, 3-hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitors) or by reducing hepatic very low density lipoprotein synthesis (gemfibrozil, nicotinic acid). LDL concentration may also be reduced by treatment with one of the fibrates (e.g., fenofibrate).

Several classes of lipid-lowering drugs also increase the plasma high-density lipoprotein (HDL) cholesterol concentration. In the case of the fibrates, this appears to be principally mediated through an increase in lipoprotein lipase activity. Gemfibrozil additionally stimulates apolipoprotein AI synthesis. The increase in HDL cholesterol produced by nicotinic acid is due primarily to decreased clearance of HDL particles from the circulation. The increase in HDL concentration produced by gemfibrozil was shown in the Helsinki Heart Study to make a major contribution to a reduced incidence of coronary artery disease, independently of that made by the decrease in LDL.

The Cholesterol-Lowering Atherosclerosis Study demonstrated that combined therapy with a resin (colestipol) and nicotinic acid can reduce the progression of coronary atherosclerosis and the development of graft lesions in patients who have undergone coronary artery bypass graft surgery.

(Am J Cardio 1990;66:16A-19A)

in discussing the pharmacotherapy of disordered lipoprotein metabolism, it is convenient to consider 2 principal moces of action of these agents. One mode is their effects on those lipoproteins whose principal function is to transport cholesterol, triglycerides, or both, from the splanchnic region (i.e., the liver and intestine) to peripheral tissues. These lipoproteins contain apolipoprotein (apo) B—apo B48 in the case of chylomicrons and apo B100 in the case of the very low density, intermediate-density and lew-density lipoproteins (VLDL, IDL and LDL, respectively). Most research into lipid-lowering drugs has centered on apo B100-containing lipoproteins. The other mode of action of these drugs is their effects on high-density lipoproteins (HDL), which play a central role in the movement of cholesterol from peripheral tissues back to the liver—a process usually referred to as reverse cholesterol transport.

EFFECTS OF DRUGS ON APOLIPOPROTEIN B-CONTAINING LIPOPROTEINS

What do we know about the metabolism of these particles and how they influence atherogenesis? The triglyceride-rich VLDLs are synthesized and secreted by the liver and are then converted to IDL in peripheral tissues through the action of endothelium-bound lipoprotein lipase (Fig. 1) The IDL particles can then undergo 1 of 2 fates: (1) They can be taken up and catabolized by the liver through and B100,E receptors, or (2) they can be converted to the sholesteryl ester-rich LDL, which is then also removed from the circulation, again primarily by hepatic apo B100,E receptors. A proportion of LDL is also catabolized through apo B100,E receptors in peripheral tissues.

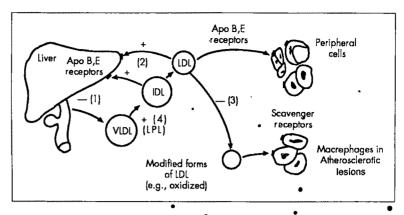
There is increasing evidence that the LDL particle itself may not be directly atherogenic. Rather, it must be converted to modified forms that exhibit atherogenic activity. Much attention has been directed toward this process, particularly the oxidation of the polyunsaturated fatty acids in LDL. This leads to secondary changes in the apo B100 of the particles, which render them recognizable by so-called scavenger receptors present in arterial matrophages. This is probably the major route by which LDL enters the macrophages in developing atherosclerotic lesions. Other forms of modified LDL have also been described (e.g., glycated forms), which may also contribute in an important way to atherogenesis.

The principal goal of lipid-lowering treatment has been to prevent coronary artery disease (CAD) by reducing the plasma corcentration of LDL. Basically, there are 4 ways in which lipid-lowering agents exert their effects on the apo B100-containing lipoproteins: (1) stimulation of LDL clearance by increased synthesis of apo B100,E

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FIGURE 1. Metabolism of apolipoprotein B100—containing lipoproteins and sites of pharmacologic intervention. The numbers 1 through 4 indicate the following: (1) inhibition of VLDL secretion (nicotinic acid, gemfibrozil); (2) stimulation of apo B100,E receptor status in liver (resins, HMG-CoA reductase inhibitors); (3) inhibition of LDL modification (probucol); (4) stimulation of lipoprotein lipase (gemfibrozil, fibrates). IDL = intermediatedensity lipoprotein; LDL = low-density lipoprotein; VLDL = very low density lipoprotein. (Reprinted with permission from Adis Press Ltd, Auckland, New Zealand.)



receptors in the liver (e.g., bile acid-binding resins [cholestyramine, colestipol], 3-hydroxy-3-methyl-glutaryl coenzyme A [HMG-CoA] reductase inhibitors [lovastatin])^{2,3}; (2) inhibition of VLDL secretion by the liver, which has a secondary effect on LDL production from VLDL (e.g., nicotinic acid, gemfibrozil)^{2,5}; (3) inhibition of LDL modification (e.g., antioxidants [probucol])⁶; and (4) stimulation of lipoprotein lipase activity (e.g., gemfibrozil, fibrates).^{5,7}

Hepatic apo B100,E receptors are a major determinant of plasma LDL concentration,8 and the stimulation of receptor synthesis is an effective mode of action in patients with hypercholesterolemia. The primary action of the bile acid sequestrants is to inhibit the reabsorption of bile acids in the terminal ileum, thereby reducing their enterohepatic recirculation. This in turn increases the activity of cholesterol-7-alpha-hydroxylase, which is suppressed by bile acids. Because this enzyme is rate-limiting in the conversion of cholesterol to primary bile acids, cholesterol oxidation to bile acids is increased. Although this is associated with a compensatory increase in cholesterol synthesis within hepatocytes, it is not sufficient to prevent an increase in the synthesis of apo B100, E receptors, which is under feedback suppression by the unesterified cholesterol content of the cells. This in turn increases the rate of uptake of LDL from the circulation and decreases the plasma LDL concentration.

The HMG-CoA reductase inhibitors also increase apo B100,E receptor activity in hepatocytes. By reducing the activity of the rate-limiting enzyme for cholesterol synthesis, they reduce the intracellular pool of unesterified cholesterol and hence increase receptor synthesis. The combination of a bile acid-sequestering resin and an HMG-CoA reductase inhibitor can be particularly effective in lowering LDL concentration by taking advantage of these agents' different modes of action on cholesterol metabolism.

Nicotinic acid and gemfibrozil reduce LDL levels through primary effects on the hepatic synthesis of VLDL. In the case of nicotinic acid, this is secondary to decreased delivery of free fatty acids to the liver from adipocytes, in which nicotinic acid inhibits the lipolysis of stored triglyceride. The mechanism of action of gemfibrozil on VLDL is not yet clear, although metabolic studies in patients with hypertriglyceridemia have shown that it involves a reduction in the rate of VLDL triglyceride synthesis.

Probucol is also used to decrease LDL levels, although its mode of action is still not clear. Interest is now focused more on probucol's antioxidant action on LDL. The fact that probucol also decreases HDL cholesterol has raised concern, although the significance of this finding will not be known until its effects on HDL metabolism are understood.

The mechanism by which a drug decreases LDL concentration is probably not important for the prevention of CAD. Reductions produced by both cholestyramine and gemfibrozil have been shown to decrease the incidence of CAD in hyperlipidemic men. 9,10 Drugs that reduce LDL production by reducing VLDL synthesis also reduce the concentrations of VLDL and IDL and are therefore of value in the treatment of patients with hypertriglyceridemia and dysbetalipoproteinemia. In addition, VLDL concentrations can be lowered by drugs that increase lipoprotein lipase activity. In some hypertriglyceridemic subjects, the associated increase in the fractional rate of conversion of VLDL to LDL can produce a transient or sustained increase in LDL levels.

EFFECTS OF DRUGS ON HIGH-DENSITY LIPOPROTEIN

In contrast to the situation with LDL, the mechanism by which drugs alter HDL cholesterol concentration is likely to be important, since a change in concentration need not necessarily be accompanied by a parallel change in reverse cholesterol transport. There are 2 reasons for this: First, cholesterol enters HDL from more than 1 source (i.e., peripheral tissues and triglyceride-rich lipoproteins); second, the concentration of cholesteryl esters in HDL reflects not only the rate of delivery of cholesterol to the particles, but also the fractional rate of catabolism of the particles and the fractional rates of transfer of cholesteryl esters from the particles to the liver and to other lipoproteins.

Nascent HDL particles are synthesized in several different tissues. The small intestine secretes particles containing apo AI, and the liver secretes particles predominantly containing apo E (Fig. 2). In addition, several peripheral tissues also secrete apo E-containing particles (e.g., macrophages). Unlike the spherical mature HDL particles found in normal plasma, the nascent particles are discoidal because of the absence of cholesteryl esters. When these particles are acted upon by the cholesterolesterifying enzyme lecithin:cholesterol acyltransferase

A SYMPOSIUM: HDL CHOLESTEROL IN CORONARY ARTERY DISEASE

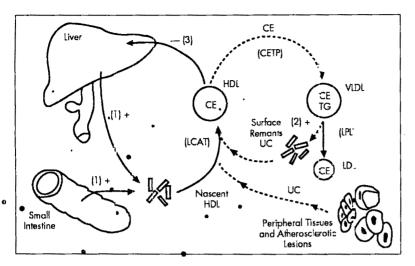


FIGURE 2. Metabolism of high-density lipoprotein (HDL) and mechanisms by which drugs increase plasma HDL cholesterol concentration. The numbers 1 through 3 indicate the following: (1) stimulation of apo A1 synthesis (gemfibrozil); (2) stimulation of lipolysis of triglyceride-rich lipoproteins (gemfibrozil, fibrates); (3) inhibition of catabolism (nicotinic acid). CE = cholesterel ester; CETP = cholesteryl ester transfer protein; LCAT = lecithincholesterol acyltransferase; LDL = low-density lipoprotein; LPL = lipoprotein lipase; TG = triglycerides; UC = unesterified cholesterol: VLDL = very low density lipoprotein. (Reprinted with permission from Adis Press Ltd, Auckland, New Zealand.)

(LCAT), and acquire additional unesterified cholestero. from tissues and as a component of the surface remnants of triglyceride-rich lipoproteins, they are converted to the mature spherical forms. However, in humans, most cholesteryl ester molecules are not retained in HDL, but are transferred by way of a transfer protein to the cores of triglyceride-rich lipoproteins such as VLDL.

Cholesteryl esters formed in HDL by the LCAT reaction are delivered to hepatocytes via several routes: (1) as a result of uptake of apo B-containing lipoproteins (chylomicron remnants, IDL and LDL); (2) by clearance of apo E-containing HDL particles from the circulation through apo B100, E receptors and apo E receptors; and (3) by direct transfer from HDL to hepatocytes by way of a mechanism that does not involve catabolism of the particles.11 •

Drugs that increase HDL cholesterol are known to do so by 1 or more of the following 3 mechanisms: (1) stimulation of the synthesis of apo AI, the major HDL proteir. (e.g., gemfibrozil, cholestyramine)^{5,12}; (2) stimulation of lipolysis of triglyceride-rich lipoproteins (e.g., gemfibrozil, clofibrate, bezafibrate)5,7,12; and (3) inhibition of the catabolism of HDL particles (e.g., nicotinic acid).4

There is strong evidence that gemfibrozil increases the synthesis of apo AI in hypertriglyceridemic subjects, pre-

Drug	Aro Al SR	FCR	LPL	HL
Cholestyramine	° †•	•		
Gemfibrozil	† † •	7440.	}	
Estrogens	↑		•	+
Nicotinic acid		+		
Fibrates	4.00	*****	↑	

FIGURE 3. Effects of some drugs and hormones on metabolic determinants of plasma high-density lipoprotein cholesterol concentration. Apo AISR = apolipoprotein AI synthesis rate; FCR = apo Al fractional catabolic rate; HL = hepatic lipase activity; LPL = lipoprotein lipase activity.

sumably leading to an increase in the synthesis of nascent HDL particles. The site of this action (i.e., liver or intestine) is not known. Cholestyramine also stimulates apo AI synthesis in humans, but to a lesser extent than does gernfibrozil. The increase in HDL cholesterol produced by gemfibrozil is also due in part to an increase in lipoproteir lipase activity. This appears to be the principal mechanism by which clofibrate and bezafibrate increase HDL chclesterol. In addition to increasing the rate of transfer of unesterified cholesterol from triglyceride-rich lipoproteins to HDL, an increase in lipoprotein lipase activity may also reduce the transfer of cholesteryl esters from HDL to VLDL by reducing the residence time of the latter in plasma. The increase in HDL cholesterol produced by nicotinic acid is due to a reduced fractional rate of catabolism of apo A-containing HDL particles, although the mechanism of this effect has not been studied. Nicotinic acid has not been found to increase the rate of synthesis of apo AI or apo AII. The known effects of some agents on HDL metabolism are summarized in Figures 2 anc 3.

The effects on reverse cholesterol transport and athercgenesis of different drug-induced modifications of HDL metabolism are likely to attract considerable attention over the next few years. Current information is not sufficient to permit any generalizations. However, it is of interest that the 2 drugs demonstrating increased apo AI syrthesis (i.e., cholestyramine and gemfibrozil) have also been shown to reduce the incidence of CAD in prospective clinical trials (the Lipid Research Clinics Coronary Primary Prevention Trial [LRC-CPPT] and the Helsinki Heart Study) through a mechanism related in part to the increase in HDL cholesterol.^{9,10} In addition, an increase in apo AI synthesis has been described in women taking estrogens, the use of which was found in the LRC-CPPT to be associated with a low incidence of cardiovascular disease in postmenopausal women.¹³ Statistical analyses indicated that this protective effect was partly explained by the associated increase in HDL cholesterol.¹³ These observations, coupled with evidence from other sources (studies of familial hypoalphalipoproteinemia, experimental studies in animals) supporting the likely importance of apo AI synthesis in conferring protection against atherosclerosis, suggest that drug-induced increases in HDL cholesterol resulting from stimulation of apo AI production are likely to have beneficial effects on reverse cholesterol transport and atherogenesis.

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Interrelationship of Triglycerides with Lipoproteins and High-Density Lipoproteins

Antonio M. Gatto, Jr., MD. DPhi

Triglycerides are transported by the largest and most lipid-rich of the lipoprotein particles, namely, chylomicrons and very low density lipoproteins (VLDL). These particles are buoyant because of the high triglyceride content, which makes up approximately 90% by weight of the chylomicron and 70% by weight of the VLDL.

The chylomicron transports exogenous or dietary fat and cholesterol, whereas VLDL transports endogenous triglyceride and cholesterol in lipoproteins synthesized and secreted by the liver. Both chylomicrons and VLDL are hydrolyzed at the capillary surface by the enzyme lipoprotein lipase. Lipoprotein lipase catalyzes the hydrolysis of triglyceride in the lipid core of these particles, producing smaller particles known as remnants. We currently believe the remnants are atherogenic and that this is one reason why hypertriglyceridemia may predispose to coronary artery disease.

Chylomicron remnants are recognized and removed by hepatic receptors that contain apolipoprotein (apo) E. The rate of clearance of remnant particles depends on which subfraction of apo E is present. Particles containing apo EII are removed more slowly than those with apo EIII and EIV.

The dietary cholesterol from the chylomicron remnant particles is thought to down-regulate the hepatic low-density lipoprotein (LDL) receptors. VLDL remnants, also called intermediate-density lipoprotein (IDL), contain apo E and may be removed by the liver through the LDL or B/E receptor. The decrease in activity of these receptors results in apparent oversynthesis of LDL, the end-product of VLDL and IDL metabolism.

LDL is the major cholesterol carrier, followed by high-density lipoprotein (HDL). LDL carries approximately up to three-fourths of the cholesterol in the blood, and about two-thirds of LDL is removed by specific LDL receptors as it circulates. The other portion is removed by low-affinity pathways. HDL contains approximately 50% cholesterol and phospholipid. HDL is synthesized in the liver the intestine and also originates from the surface of chylomicrons and VLDL during lipolysis. HDL acquires cholesterol from peripheral tissues and is es-

terified by the lecithin cholesterol acyltransferase or LCAT to cholesteryl ester. The cholesteryl ester may then be transferred from HDL to LDL, IDL or VLDL by the cholesteryl ester transfer protein. Thus, cholesterol can be transported to the liver indirectly by HDL, and HDL fractions containing apo E may directly transport HDL to the liver. HDL exists in a nascent form before being converted into spherical particles. There is some evidence that apo Al may play a particularly important role in this reverse cholesterol transport process.

HDL may be subdivided in several ways: one based on its apoprotein content and one based on its density (e.g., HDL2 and HDL3). In hypertriglyceridemia, the formation of HDL from the hydrolysis of triglyceride-rich particles may be diminished. In addition, when postprandial lipemia occurs, or when there is a prolonged elevation of triglyceride-rich lipoproteins, an increased transfer of triglyceride from triglyceride-rich lipoprotein particles into LDL and HDL may occur in exchange for cholesteryl ester. The metabolic changes associated with hypertriglyceridemia may decrease the concentration of HDL and result in small, dense particles of LDL and HDL.

(Am J Cardiol 1990:66:20A-23A)

ipoproteins transport lipics in 3 separate ways: the exogenous pathway, the endogenous pathway and the reverse cholesterol pathway. We will focus on the first 2 of these routes, by which cholesterol and the triglyceride-rich lipoproteins (chylomicrons and very low density lipoproteins [VLDL] are metabolized.¹

Exogenous pathway: Dietary cholesterol is absorbed into the intestinal wall and packaged into particles called chylomicrons. Apolipoprotein (apo) B48, a truncated form of the apc B100 made in the liver, is incorporated into the chylomicrons. Two other apos—apo E and CII—are added to the chylomicrons either in the lymph or after these particles reach the circulation. Apo CII is required for activation of the enzyme lipoprotein lipase (LPL), which catalyzes triglyceride hydrolysis in the lipid core of the chylomicron and results in smaller particles known as chylomicron remnants. Apo E is required for recognition of these remnants by the hepatic receptors.

There are 2 ways in which triglycerides interact with high-density lipoprotein (HDL): First, the cholesteryl ester and triglycerides are exchanged between the chylomicron remnant and HDL (Fig. 1). LPL is attached to receptors on the surface of capillary endothelial cells; the

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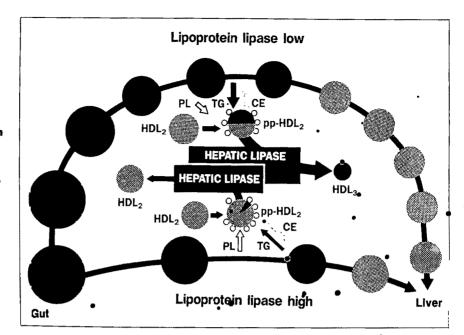


FIGURE 1. The interaction between triglycerides and high-density lipoprotein (HDL) cholesterol in the presence of lipoprotein lipase. CE = cholesterol ester; PL = phospholipase; pp =postprandial; TG = triglycceride.

higher the concentration of LPL, the more rapidly these chylomicron particles are removed from the blood. Second, as the chylomicrons are broken down and the triglycerides are attacked by LPL, surface components from the chylomicron particles are transferred to and incorporated into HDL, increasing the mass of the HDL particle.

The concentration of LPL correlates positively with the concentrations of HDL and its subfraction HDL₂.² When LPL activity is increased, chylomicron particles will be cleared from the circulation more rapidly, so that endothelial cells will not be exposed to these particles. Several factors can influence the activity of LPL. Exercise increases LPL activity, whereas cigarette smoking has the opposite effect. The affinity of this enzyme for the chylomicron particle also appears to be increased by estrogen. Finally, LPL activity is insulin-dependent.

As triglycerides are being hydrolyzed from the core of the chylomicron and the surface components are being transferred to HDL, the now smaller chylomicron remnant remains to carry dietary cholesterol to the liver. Apo E on the remnant surface is then recognized by hepatic apo E receptors, so that the particles will be removed from the circulation and taken up by the liver cells. The rate of clearance depends on the subfraction of apo E present (i.e., particles containing apo EIV are removed more quickly than those containing apo EII). This uptake and removal process is significant in that it is believed to increase the cholesterol level within the liver, thus down-regulating the hepatic low-density lipoprotein (LDL) receptors and increasing the amount of circulating LDL cholesterol.

Endogenous pathway: Lipoprotein transport begins with the synthesis of VLDL by the liver. VLDL, which contains apo B100, CII and E, is also converted by LPL to a smaller particle or remnant, called intermediate-density lipoprotein (IDL). As IDL is converted to LDL,

apo C and E are transferred to HDL. These remnants (about 40% of VLDL) can be removed directly by the hepatic LDL-receptors through apo E binding, whereas LDL is removed by LDL-receptors binding to apo B100. About two-thirds of the LDL is believed to be removed by this mechanism; the other one-third is taken up by peripheral tissues involving so-called low-affinity pathways. Observations in an animal model (Watanabe rabbits) of familial hypercholesterolemia suggest that oxidized LDL is more rapidly taken up by these low-affinity or macrophage receptors in the arterial intima and thus contributes to the development of atherosclerotic plaque.³

In the process of converting the triglyceride-rich lipoproteins (the chylomicrons and VLDL) to chylomicron remnants and IDL or LDL, respectively, the apos become the key determinants of the structure and density of each particle. Apos are lost from the surface of lipoprotein particles and, along with cholesterol and phospholipid, are transferred to HDL. In the end, LDL contains only 1 large apo, B100, which directs it to the B/E or LDL receptor. LDL levels can be increased owing to deficiencies or abnormalities of the B/E receptor.

There are at least 4 different sources of HDL (Fig. 2):
(1) the chylomicrons and VbDL, which may be considered together; (2) the intestine, which secretes the apos associated with phospholipid that constitute a nascent form of HDL; (3) the liver, which also secretes a nascent form of HDL; (4) the macrophages within the arterial wall, which can secrete an apo E and phospholipid particle that may serve as another nascent form of HDL. Thus, if one inhibits LPL activity or interferes with the breakdown of triglyceride-rich lipoproteins, HDL mass will be decreased and there will be less HDL in the blood.

Nascent HDL particles can take up cholesterol from the peripheral tissues, after which the enzyme lecithin cholesterol acyltransferase, or LCAT, converts the cho

A SYMPOSIUM: HDL CHOLESTEROL IN CORONARY ARTERY DISEASE

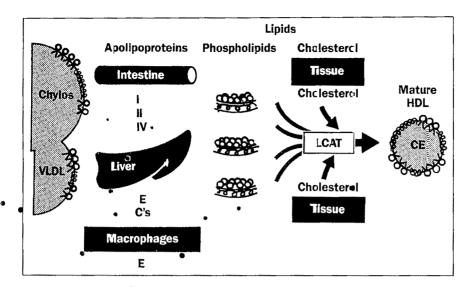


FIGURE 2. Origin of high-density lipoprotein (HDL) cholesterol. There are at least 4 different sources: (1) the chylomicrons (Chylos) and very low density lipoprotein (VLDL), (2) the intestine, (3) the liver, and (4) arterial wall macrophages. CE = cholesterol ester; LCAT = lecithin cholesterol acyltransferase.

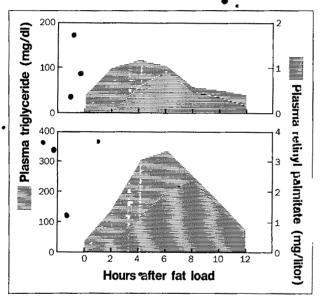


FIGURE 3. Postprandial peaks of both triglyceride and plasma retinyl palmitate (a marker of chylomicron remnants) are higher in the lipoprotein lipase-deficient group (bottom) compared with the control group (top). (Reprinted with permission from Med Clin North Am.5)

lesterol to cholesteryl ester. The buildup of cholesteryl ester within the HDL particle in turn transforms the nascent HDL into a mature spherical particle. Schaefer and Levy⁵ described a group of patients with CAD who had lipoprotein profiles typical of persons with a relative deficiency of LPL: slightly increased LDL, increased triglycerides and VLDL and low HDL.

POSTPRANDIAL LIPEMIA: RESULTS OF A STUDY

To help clarify the role of LPL in triglyceride disposition, a small series of patients was studied in a joint effort by Joseph Patsch at the University of Innsbruck and

TABLE | Perspective from Framingham

Patients with high TG levels may be at high risk for CHD Patients with very low TG/HDL cholesterol ratios are an exception ~10% of these patients have a low (<3.5) ratio 90% of patients with high TG levels are at high risk, ~50% will have a total cholesterci level <250 mg/dl

CHD = coronary heart disease; HDL = high-density lipoprotein; TG = triglyceride. Adapted from Castelli⁶

Wolfgang Patsch at Baylor College of Medicine. They compared the levels of triglycerides and chylomicron remnants after a typical meal in healthy subjects. Postgrandial peaks of both plasma triglyceride and plasma retinyl palmitate (a marker of chylomicron remnants) were higher in the subjects who also had lower levels of LPL (Fig. 3). These investigators had shown that patients with lower LPL levels also had lower blood levels of HDL.

The 2 investigators also carried out a case-control study involving healthy subjects and patients with CAD. To enter the study, patients had to have angiographically cocumented CAD (2- or 3-vessel disease with >75% narrowing), with LDL level <175 mg/dl and triglyceride Evels <250 mg/dl. All subjects were given a standardized fat meal containing 130 g of fat per square meter of body surface area. Using retiny palmitate measurements taken 2 weeks apart, the investigators found a strong correlation in the magnitude of postprandial lipemia Emong the patients with CAD. These findings suggest that CAD may be induced by anomalies in the metabo-Esm of triglyceride-rich lipoproteins.

RELATION BETWEEN TRIGLYCERIDES AND CORONARY ARTERY DISEASE

Are triglycerides an independent risk factor for CAD? The available evidence suggests that this is the case in women. High triglycerice levels may predispose to atherosclerosis in several ways: (1) they may result in low

levels of HDL; (2) they may result in small, dense LDL particles that are more atherogenic; and (3) the remnants themselves may directly damage the arterial vessel wall. However, the question remains, are these factors causally related or are they markers of the presence of other conditions such as diabetes mellitus, low HDL or obesity? In multivariate analyses, the association between triglycerides and CAD tends to weaken or disappear.

The results of The Framingham Study suggest that persons with high levels of triglycerides are at greater risk for CAD (Table I).⁶ The data also indicate that triglycerides are an independent risk factor in women.

Based on our research, we believe that hypertriglyceridemia and CAD are related and that the risk definitely increases (1) when cholesterol levels are high, (2) in the presence of familial combined hyperlipidemia or dysbetalipoproteinemia, (3) when HDL level is low, and (4) in the presence of a condition known as hyper-apo B. Hypertriglyceridemia is also a risk factor for CAD in those with a strong family history of premature coronary disease or in the presence of other risk factors such as smoking, hypertension, obesity or diabetes.

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Predictive Value for Coronary Heart Disease of Baseline High-Density and Low-Density Lipoprotein Cholesterol Among Fredrickson Type IIa Subjects in the Helsinki Heart Study

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In the Helsinki Heart Study 2,590 subjects (63.5% of total) had a type IIa hyperlipoproteinemia at screening. Baseline low-density lipoprotein (LDL) cholesterol (mean 193 mg/dl; 5 mmol/liter) and high-density lipopratein (HDL) cholesterol (mean 50.2 mg/dl: 1.3 mmol/liter) showed no statistical correlation (r = 0.046). Both the placebo (1,293 patients) and gemfibrozil groups (1,297 patients) were divided into tertiles by baseline HDL and LDL cholesterol to determine the relative predictive risk of developing coronary artery disease.

In a population with elevated LDL cholesterol, it is significant that the lipoprotein fraction with the greatest predictive value was HDL cholesterol. The severity of LDL cholesterol elevation did not provide any differential predictive value for coronary artery disease.

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The National Cholesterol Education Program has highlighted the use of total serum cholesterol levels for initial classification and plasma low-density lipoprotein (LDL) cholesterol for subsequent management of patients at risk of coronary artery disease (CAD). After a minimum of 6 months of diet therapy, a persistently elevated LDL cholesterol ≥190 mg/dl (4.9 mmol/liter) is said to indicate a need for pharmacologic treatment. The report is remarkable in its assertion that additional risk factors influence the management of the patient only in the borderline to high-risk LDL cholesterol group (160 to 189 mg/dl or 4.1 to 4.9 mmol/liter), thereby implying that plasma LDL cholesterol is the only significant lipid marker for predicting subsequent CAD. However, many studies have shown high-density lipoprotein (HDL) cholesterol to be an independent predictor of subsequent CAD.2-5 The 5-year Helsinki Heart Study demonstrated a 34% reduction (p = 0.02) in incidence of cardiac end points, which was correlated with the increase in HDL cholesterol and to a lesser extent the decrease in LDL cholesterol. 5,6 The objectives of the present analysis of the Helsinki Heart Study data are to determine in those subjects with Fredrickson type IIa hyperlipidemia whether baseline HDL or LDL cholesterol was a better predictor of subsequent cardiac end points, and what influence gemfibrozil had on the incidence of end points at different levels of the respective lipids.

METHODS

Patients: Entry into the Helsinki Heart Study required subjects with no evidence of CAD to fulfill a single lipid criterion on 2 consecutive screening visits: a fasting non-HDL cholesterol level >200 mg/dl (5.2 mmol/liter). From the screened population, 4.081 subjects were randomized into the study, of which 63% (2,590 subjects) had a lipid disorder classified as Fredrickson type IIa, defined as an LDL cholesterol level >175 mg/dl (>4.5 mmol/liter), and a total triglyceride level <177 mg/dl (<2 mmol/liter) at the second screening visit. Baseline lipid values (HDL cholesterol and total cholesterol) were determined at the intervention visit when subjects were randomized to receive either placebo or gemfibrozil, and LDL cholesterol was estimated by the Friedewald equation using the fasting total triglycerides from the second screening visit. In the interval between the second screening visit, when each subject was classified as Fredrickson type IIa, IIb or IV, and the intervention visit, when base-

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TABLE I Baseline Lipid Values and Cardiac End Points by Baseline HDL Cholesterol Tertiles

	HDL-C Tertile (mg/dl)				
	<44.9	44.9-53.7	≥53.7		
Placebo (n)	413	419	465		
HDL-C (mg/dl)	39.4	48.9	62.1		
LDL-C (mg/dl)	194	194	192		
Triglycerides (mg/dl) Cardiac end points	131	120	112		
n (%)	22 (5.33)	17 (4.06)	5 (1.08)		
Gemfibrozil (n)	423	455	415		
HDL-C (mg/dl)	38.9	48.9	61.8		
LDL-C (mg/dl)	194	195	192		
Triglycerides (mg/dl) Cardiac end points	131	118	110		
n (%)	13 (3.07)	13 (2.86)	7 (1.67)		

line lipid values were established, total cholesterol values decreased 6.7%. For this reason, some subjects had LDL cholesterol values <175 mg/dl (<4.5 mmol/liter). Fasting lipids were estimated at 6-month intervals during the trial. The criteria and procedures for determining cardiac end points (myocardial infarction and cardiac deaths) are described elsewhere. No statistical hypothesis testing was performed in this post-hoc analysis. For descriptive purposes, baseline LDL and HDL cholesterol levels were divided into tertiles, each range representing a third of the subjects in the population with type IIa hyperlipidemia.

RESULTS

The overall mean (\pm standard deviation) lipid values for the type IIa subjects entering the Helsinki Heart Study were as follows: HDL cholesterol 50.2 ± 10.7 mg/dl (1.30 ± 0.28 mmol/liter) and LDL cholesterol 193.3 ± 31.4 mg/dl (5 ± 0.81 mmol/liter). There was no correlation between baseline LDL level and baseline HDL level (r = 0.046).

Baseline high-density lipoprotein cholesterol tertiles: In Table I, the 2 groups are divided into tertiles based on baseline HDL cholesterol level. LDL cholesterol values are similar in each group. The mean HDL cholesterol in the low HDL group is 39 mg/dl (1.60 mmol/liter), in the middle group 49 mg/dl (1.27 mmol/liter), and in the high group 62 mg/dl (1.60 mmol/liter). The mean total triglyceride values show an inverse correlation with HDL cholesterol. The incidence of cardiac end points in the placebo group for the low, middle and high tertiles of HDL cholesterol are 5.33, 4.06 and 1.08%, respectively. The corresponding values for the gemfibrozil group are 3.07, 2.86 and 1.67%.

Five known cardiac risk factors (age, smoking, body mass index, alcohol intake and blood pressure) are detailed for each tertile in Table II. HDL cholesterol is clearly associated with alcohol intake and demonstrates an inverse relationship to tobacco consumption. In addition, there is a trend toward an increased body mass index

TABLE II Type IIa Subjects: Cardiovascular Risk Factors by Baseline HDL Cholesterol Tertiles

	HDL-C Te	ertile (mg/dl)		
	<44.9	44.9–53.7	≥53.7•	
Age (yr)	•	V (V		-
Gemfibrozil	47.4	47.4	47.3	
Placebo	47.1	47.9	47.5	
Smokers (%)				
Gemfibrozil	38.8	3 2 .5	26.8	
Placebo	38.0	35.7	28.2	
ВМІ				
Gemfibrozil	26.6	26.0	25.8	
Placebo •	26.4	26.1	25.6	
Alcohol intake (cl/yr	•	•		
Gemfibrozil	257	325	405	
Placebo	261	317	434	
Systolic BP (mm Hg)	•		•	
Gemfibrozil	135	135	136	
Placebo	134	136	136	
Diastolic BP (mm Hg) 1	•		
Gemfibrozil •	88	87	88	
Placebo	87	89	88	

BMI = body mass index; BP = blood pressure; cl = centiliters of absolute alcohol per year; HDL-C = high-density lipoprotein cholesterol.

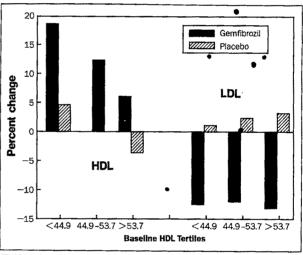


FIGURE 1. Change in plasma lipids by baseline high-density lipoprotein (HDL) cholesterol tertiles. LDL-C = low-density lipoprotein cholesterol.

in the low HDL cholesterol tertile. Figure 1 shows the percentage change from baseline in HDL and LDL cholesterol after 6 months of treatment. There was a small but consistent increase in LDL cholesterol of 1 to 2.9% in the placebo group and a consistent decrease of 11.8 to 12.5% in the gemfibrozil group. The percentage change in LDL cholesterol was not influenced by the baseline HDL cholesterol was clearly dependent on the baseline HDL cholesterol in values for both the gemfibrozil and placebo groups. The changes in HDL cholesterol in the placebo group indicate a regression toward the mean, unlike the gemfibrozil group in which HDL cholesterol increased at all baseline levels.

TABLE III Baseline Lipid Values and Cardiac End Points by Baseline LDL Cholesterol Tertiles

	LDL-C Tertile (mg/dl)			
•	<178.4	178.4–204.3	≥204.3	
Placebo (n)	428	434 *	435	
HDL-C (mg/dl)	51.0	50.7	50.1	
LDL-C (mg/cl)	161	190	227	
Triglycerides (mg/cl) Cardiac end points	126	117	119	
n (%)	14 (3.27)	13 (3.00)	17 (3.91)	
Gemfibrozil (n)	439	440	414	
HDL-C (mg/dl)	50.7	49.3	49.3	
LDL-C (mg/cl)	162	192	229	
Triglycerides (mg/cl) Cardiac end points	120	119	120	
n (%)	9 (2.05)	14 (3.18)	10 (2.42)	

TABLE IV Type IIa Subjects: Cardiovascular Risk Factors by Baseline LDL Cholesterol Tertiles

•	LDL-C Terti	le (mg/d.)	
•	<178.4	178.4-204.3	≥204.3
Smokers (%)			
Gemfibrozil	31.3	32.6	33.8
Placebo	348	31.3	35.2
BP (mm Hg)	•		
Gemfibrozil	134/86	135/88	136/89
Placebo	136/87	135/88	135/88
Alcohol intake (cl/yr	9	,	•
Gemfibrozil	348	318	319
Placebo	356	328	339
Age (yr)			
Gemfibrozil	47 3	47.4	47.5
Placebo	47 3	47.3	47.9
BMI			
Gemfibrozil	26 2	26.2	25.9
Placebo	26 0	25.9	26.2

BMI = body mass index BP = blood pressure; cl = centiliters of absolute alcohol peyear; LDL-C = low-density lipoprotein cholesterol.

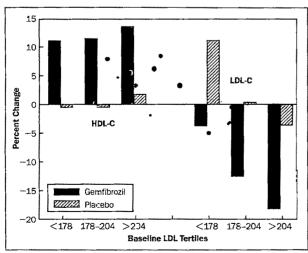


FIGURE 2. Change in plasma lipids by baseline low-density lipoprotein (LDL) cholesterol tertiles. HDL-C = high-density lipoprotein cholesterol.

Baseline low-density lipoprotein cholesterol tertiles:

The population was divided by baseline LDL cholesterol level into tertiles (Table III). HDL cholesterol levels were similar in each group (mean value 50 mg/dl [1.29 mmol/ liter]). Values for LDL cholestercl in the low group were 161 mg/dl (4.2 mmol/liter), in the middle group 190 mg/dl (4.9 mmol/liter), and in the high group 227 mg/dl (5.9 mmol/liter). Total triglycerides were approximately 120 mg/dl (1.4 mmol/liter) in all groups. The incidence of cardiac end points in the placebo group for the low, middle and high tertiles of LDL cholesterol were 3.27, 3 and 3.91%, respectively. The corresponding values for the gemfibrozil group were 2.05, 3.18 and 2.42%. Unlike HDL cholesterol, none of the 5 risk factors (Table IV) showed a correlation with increasing levels of LDL cho-

The percentage changes in HDL and LDL cholesterol after 6 months are listed in Figure 2. There was no change in HDL cholesterol in the placebo group in contrast to the gemfibrozil group, which showed an 11.6 to 13.6% increase that was not dependent on the baseline LDL value. The change in LDL was markedly dependent on the baseline values. In the placebo group there was a marked regression to the mean value with LDL cholesterol increasing 10.6% in the low tertile and decreasing 4.2% in the high tertile. LDL cholesterol decreased in all 3 tertiles in the gemfibrozil-treated group, ranging from 4.5% in the low tertile to 17.9% in the high tertile. The percentage difference in the change of LDL cholesterol between the placebo and gemfibrozil groups was a constant 14% across the range of baseline LDL values in favor of gemfibrozil.

DISCUSSION

The use of a single criterion modified by a series of risk factors has found traditional value in the practice of preventive medicine; diastolic blood pressure and plasma glucose concentration are 2 examples. Where 2 independent criteria exist, one exerting a negative and the other a positive predictive value in disease cutcome, it becomes more difficult to arrive at simplistic treatment guidelines. Follow-up data on the relative risk of CAD from the Framingham Heart Study clearly showed the protective effect of a high HDL cholesterol level despite abnormally elevated levels of total cholesterel, which in themselves, would have justified pharmacologic intervention.8 In the Lipid Research Clinics Coronary Primary Prevention Trial, there was a twofold difference in the incidence of subsequent CAD between the highest and lowest tertiles of baseline HDL chclesterol despite LDL cholesterol values of >175 mg/liter (>4.5 mmol/liter) at entry into the study. It was also noted that cho estyramine exerted the least benefit in reducing the incidence of CAD in subjects with low HDL cholesterol levels at baseline; these subjects proved to be at the greatest risk of CAD among the study participants. The data from the Helsinki Heart Study confirm these earlier findings, with a fivefold difference in the incidence of CAD between the highest and lowest tertiles of baseline HDL cholesterol despite similar baseline LDL levels. More importantly, the benefit of gemfibrozil therapy in increasing HDL and reducing

LDL cholesterol was most marked in the tertile with the highest risk of CAD (i.e., the tertile with the lowest HDL cholesterol values). There was a 42% reduction in the incidence of CAD in the gemfibrozil group compared with the placebo group in the lowest HDL cholesterol tertile.

The level of HDL cholesterol is affected by tobacco and alcohol consumption, and to a lesser extent, by body mass index. The relation between baseline lipid values, treatment group and the incidence of cardiac end points was investigated for the entire study population using the Cox proportional hazards model. Smoking status and quartile of alcohol consumption were included among other risk factors for CAD as fixed covariates in the model. Baseline HDL (p <0.0001), LDL (p <0.001) and treatment group (p <0.03) had significant correlations. In contrast, baseline triglycerides showed no correlation (p <0.77). Despite the correlation between tobacco and alcohol consumption and HDL cholesterol, HDL cholesterol clearly remains an independent risk factor.

Whereas it is important to identify persons at high risk of subsequent CAD, it is equally important to avoid unnecessarily aggressive therapy indicated solely by an elevated LDL cholesterol value. It is clear that increasing low HDL cholesterol by cessation of smoking, reduced body weight, increased exercise and pharmacologic therapy, when appropriate, are equally important as the reduction of elevated LDL cholesterol.

The role of HDL cholesterol in the management of hypercholesterolemia was reviewed by the National Cholesterol Education Program Committee, who reaffirmed as appropriate the current perspective. Treatment guidelines need to reflect the importance of HDL cholesterol, not only in the borderline high range of LDL cholesterol, but also equally at high levels.

CONCLUSION

Within the type IIa population studied in the Helsinki Heart Study, baseline HDL cholesterol was a better predictor of subsequent cardiac end points than baseline LDL cholesterol. Subjects with low baseline HDL cholesterol values were at high risk of cardiac end points, whereas those with high HDL values were at low risk of cardiac end points despite similarly elevated LDL values. Gemfibrozil reduced the incidence of cardiac end points by 42% compared with placebo in the group with HDL values <45 mg/dl (<1.16 mmol/liter).

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Discussion

Question: How many patients would need to be treated for how long in order to save one life?

Dr. W. Virgil Brown (Washington, DC): The answer to that question depends on many unspecified factors, such as how well the patients are treated and how high the risk in the population in question. At the end of the 7-year Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT), almost one third of the participants had CAD according to established criteria, and 187 very serious events occurred, including both myocardial infarction and sudden death. Among the patients given placebo, 126 underwent coronary artery bypass grafting. Some patients experienced angina. So, I think it is important to consider the risk for coronary disease and not just the death rate.

Question: In some cases, lowering total cholesterol and LDL also causes a reduction in HDL, so that the total cholesterol HDL ratio may increase. What is the significance of this and why didn't the NCEP advocate the use of ratios in setting up their guidelines?

Dr. Rifkind: That exemplifies a paradox with respect to managing HDL. It is fairly clear that a low-fat diet will 'effectively lower LDL. Among vegetarians and in certain populations, such as the Japanese, LDL decreases to a greater extent than does HDL. Since these groups are at low risk for CAD, confusion arises in that a low HDL does not necessarily have the same significance as it does in other contexts. Nevertheless, for now, we think that the focus should be on reducing LDL, and that a consequent decrease in HDL is tolerable.

As for the second part of that question, since both HDL and LDL are predictors of CAD risk, knowing both values allows one to predict risk with greater certainty. Although I have no fundamental objection to the use of ratios, they are associated with problems at their extremes. The NCEP prefers to use the individual values of the lipoproteins.

Question: How can one justify extrapolation of the results from the Helsinki Heart Study, which involved middle-aged men with high cholesterol values, to younger persons, those with lower total cholesterol values, and women of any age? . *

Dr. Brown: Certainly whenever guidelines are issued, they should not take the place of good clinical judgment. Each patient should be evaluated based on a variety of parameters, age being only one of them, physical condition being another. Still, I think the NCEP Guidelines can be applied to everyone. We know that the risk relationships hold for women; although they are not as strong for total cholesterol as a woman gets older, they do hold for HDL and LDL into the seventh and eighth decaces. In the LRC-CPPT, results of treatment were not associated with age: the reductions in CAD among men in their late 50s were similar to those among men in their early 40s, indicating that benefits can accrue even after atherosclerotic changes have probably already taken place.

With respect to cholesterol values, the Cholesterol-Lowering Atherosclerosis Study (CLAS), undertaken arnong middle-aged men who had undergone coronary artery bypass grafting, showed that the average values were the same as those in men in Framingham who experienced a coronary event (i.e., 244 mg/dl). Extrapolations to other populations are based not only on the male cl_nical trials but also on animal models, in which high cholesterol levels led to CAD in both female and male species. Finally, heart disease is the number one cause of death in womer as well as men. Would it be rational to postpone treatment in women just because there have been no long-term clinical trials in this population? According to the NCEP's Adult Treatment Panel, the answer is no.

Question: What are the effects of low total cholesterol level on total mortality, that is, death from all causes and not just from CAD? For example, is there a relationship between low cholesterol and cancer or, as discussed in the Helsinki Heart Study, intracranial hemorrhage?

Dr. Brown: There is no question that cross-sectional studies in many different populations have shown that persons with extremely low total cholesterol levels do less well than those with slightly higher total cholesterol leve.s. We have to consider the effects of other conditions or d.sease states on the metabolic system involving lipid transport. If a population is monitored for only 2 years and then mortality is assessed, it is difficult to know what other factors may have been at work. For example, a patient may have had occult cancer at the time of entry, which both lowered cholesterol and caused death by other means. Cigarette smokers, as a group, tend to have lower body weight and lower levels of cholesterol. With respect to hemorrhagic stroke, there were no data in the LRC-CPPT correlating low total cholesterol or HDL levels with this event, although there are data from communitybased studies that indicate low cholesterol in hypertensive populations is associated with intracranial hemorrhage. This is not explained by present data.

Question: Is there a linear relationship between alcohol consumption and HDL levels, or does HDL increase with only small amounts of alcohol, as was originally reported? What about differential effects of alcohol on HDL subfractions?

Dr. Rifkind: Undoubtedly there is a direct relationship between the amount of alcohol consumed and the level of HDL. This finding has been consistent among several major trials. As to which HDL subfractions are affected, there has been some controversy. It was first suggested that HDL₃, the subfraction not correlated with CAD, was particularly affected by alcohol intake; however, more recent reports say that HDL₂ is affected. Although this issue has not yet been resolved, I can say with assurance that none of us would advocate the use of alcohol as ε means of increasing HDL. Obviously, in addition to teing an addictive drug, alcohol has many toxic effects,

and therefore, more hygienic therapeutic measures would be preferable.

Question: Suppose a patient had the following lipid profile: Total cholesterol 279 mg/dl, LDL 173 mg/dl and HDL 78 mg/dl. After some intervention, either diet modification or probucol therapy, these values decreased to 230, 150 and 58 mg/dl, respectively. Would you consider that this patient had benefited from treatment?

Dr. Brown: It's difficult to say, since no study has addressed that issue. We don't as yet know the long-term effects of treatment with probucol. Although it might help in theory, there are certainly cases in which this drug has had adverse effects on the lipid profile. For such a patient, I would look carefully at changes in lifestyle, since we cannot assume that the patient is not at risk just because the HDL level is high. Family history should also be considered. Certainly dietary therapy and hygienic measures such as weight loss and exercise should be initiated. In my opinion, at this time, drug therapy would not be indicated.

Question: If a patient has an average or slightly high LDL level but a very low HDL level, should we intervene if there is no evidence of heart disease or if the patient has already had a myocardial infarction?

Dr. Rifkind: I would say we should intervene in both cases. Although I have argued against treating a patient with isolated low HDL, this finding does increase the risk for CAD. Just as the NCEP's Adult Treatment Panel advocates more aggressive steps to reduce LDL when a patient is also hypertensive or a smoker, I think the presence of a low level of HDL should signal us to treat the LDL more aggressively. In the case of the postinfarction patient, you are dealing with a person who already has severe atherosclerosis and CAD, even with this average level of LDL. Aggressive treatment would therefore be in order, especially since the HDL level is low.

Question: In light of the CLAS, in which HDL was substantially increased, and the LRC-CPPT, in which lowering LDL in patients with HDL values <35 mg/dl provided no benefit, do you think HDL must be moderately high to achieve atherosclerotic regression?

Dr. Brown: I don't think that question can be answered fully at this time. However, I think the HDL level is extremely important. Although it was not stipulated in the NCEP Guidelines, HDL should certainly be measured in patients with CAD, since it is useful in determining treatment. I agree with Dr. Rifkind that LDL should be reduced aggressively, particularly in patients with low HDL levels.

Question: Why is probucol not recommended for patients with familial lipoprotein abnormalities?

Dr. Ernst Schaefer* (Boston, Massachusetts): As an antioxidant, probucol may prevent the modification of LDL and in that way decrease the amount of LDL taken up by macrophages. Unfortunately, we do not have prospective data on this drug. In Sweden, a study is under

way that is addressing the effects of probucol on peripheral vascular disease; results should be available in about 2 years. The problem with probucol is that it lowers HDL more than it lowers LDL. Until we have more information to indicate probucol's benefits, there is little to recommend its use in the outpatient setting.

Question: Does the means by which HDL increases affect the patient's relative risk for CAD?

Dr. Peter W.F. Wilson (Framingham, Massachusetts): I don't think we have the answer to that question at this time. Most of the studies assessing the benefits of intervention have used exercise to increase HDL levels. Moreover, they have not used heart disease as an end point. Interestingly, almost all factors that tend to increase HDL also tend to depress triglyceride levels, with two notable exceptions: alcohol and estrogen. For this reason, changes in lifestyle designed to increase HDL may influence other risk factors in a negative way, so we have to look at the bigger picture.

Question: Would you comment on the accuracy of HDL measurements and laboratory standardization?

Dr. Wilson: Programs for standardizing lipid measurements come from the Centers for Disease Control. Several hundred laboratories are participating in these programs in the United States; their primary concern is total cholesterol, for which the target for accuracy and precision has a 3% range of error. This means that if the first value measured was 200 mg/dl, the next 100 measurements should all fall within the range of 194 and 206 mg/dl. In actuality, the error rate is less than 1%. At a community hospital laboratory, you would typically get an error of 7 to 10% for total cholesterol. It is the goal of the NCEP to improve the level of accuracy throughout the United States over the next several years.

In terms of HDL, the answer is more difficult. Even under the best conditions, the laboratory error will be greater than it is for total cholesterol. To offset this, I recommend two or three measurements taken over a few weeks

Question: What about a male patient who has a myocardial infarction at age 40? His total cholesterol level is about 200 mg/dl and his HDL level is 25 to 30 mg/dl.

Dr. David Canter (Ann Arbor, Michigan): Do as much as possible to increase the HDL level, including pharmacologic measures.

Question: What is the value of monitoring creatine phosphokinase (CPK) in the patient being treated with gemfibrozil plus lovastatin if there are no symptoms of myositis? If the patient does experience myositis, would you rechallenge the patient using this combination of drugs at a lower dosage or try either drug alone?

Dr. Schaefer: Although the incidence of myositis with either gemfibrozil or lovastatin alone is only about 1%, it increases to 7% when these drugs are given together. It's important to obtain a baseline CPK measurement, since patients may remain asymptomatic when they first start taking the drug, and an early CPK value might be misleading. I have noted a greater problem with liver toxicity when patients are taking nicotinic acid and lovastatin, whereas the combination of gemfibrozil and lovastatin is generally better tolerated. Because many patients have

^{*}Ernst J. Schaefer, MD, is Chief of the Lipid Metabolism Laboratory at the Human Nutrition Research Center, Tufts University, Boston, Massachusetts. Dr. Schaefer was a faculty member at this symposium; however, data from his presentation are not included in this supplement.

side effects with nicotinic acid or the bile acid-binding resins, it would be wise to alter the dosage of the gemfibrozil/lovastatin combination to try to prevent myositis.

Question: Does taking gemfibrozil before meals decrease the efficacy of lovastatin taken with meals?

Dr. Canter: I don't have enough information to determine whether these drugs interact, but gemfibrozil should always be taken before meals.

Question: Should HDL samples drawn in the office be frozen while awaiting analysis?

Dr. Wilson: The ideal approach to performing a lipid profile is draw the sample, refrigerate it and separate out the plasma within 12 hours; total cholesterol, HDL and triglycerides should then be measured within 3 or 4 days. For small or individual studies, there is no reason to freeze the samples; however, for large-scale studies, resources may not be in place for immediate measurements, so it has been suggested that the sample be precipitated before freezing. HDL can be measured later using the supernatant. Temperatures for freezing should be around -70°C—much colder than the -20° of most freezersand the samples will probably not begin to deteriorate for at least 6 months; after 6 months, values may not be as reliable. For best results, HDL should be measured on a fresh sample, but apolipoproteins can probably be measured long after freezing without a problem.

Question: Although the major change in the Helsinki Heart Study was a 40% decrease in triglyceride levels, the statistical analysis indicates that triglycerides are not a risk factor for CAD. Are the statistical tools faulty or somehow affected by individual variability in triglycerides?

Dr. Capter: That's the problem with analyzing triglycerides: multiple risk factors must be included in the statistical model. Triglycerides show a strong correlation with HDL; in the Helsinki study, HDL was less variable than the triglycerides. When HDL is included in the analysis, any correlation between triglycerides and the incidence of CAD disappears. Some investigators still believe that triglyceride levels should be considered a risk factor, and that the methods in the Helsinki Heart Study did not allow that hypothesis to be confirmed because not all the participants had high triglyceride levels; in fact, the majority had normal levels.

Question: Does increased triglyceride levels associated with bile acid-binding resins require treatment?

Dr. Schaefer: If the patient has high VLDL and LDL or high total cholesterol and triglycerides, a resin would generally not be the first choice of therapy. Nicotinic acid would be preferable. However, if nicotinic acid is not tolerated, a resin in combination with gemfibrozil can be presented to improve tolerance.

Question: What about the effect of nicotinic acid on blood sugar levels? Does the increase in serum glucose lessen the benefit of this agent for reducing CAD risk?

Dr. Schaefer: Glucose intolerance or high insulin levels contraindicates the use of nicotinic acid. A possible exception is the patient already taking insulin who can handle an increased dose while on such therapy.

Question: A recent report on autopsy findings in the Honolulu Heart Study indicated that the presence of

coronary artery lesions was not related to HDL levels. Any comments?

Dr. Wilson: I'm not sure why there would be a difference between those results and their earlier findings. Perhaps there were too few autopsies to provide statistically significant results.

Question: Some patients treated with gemfibrozil show increases in both LDL and HDL. Should the drug be continued if the LDL level increases?

Dr. Canter: This occurs typically in the patient with a very low LDL and elevated triglycerides. The explanation is that the composition of the LDL is changing. Dr. Scott Grundy, at the University of Texas Southwestern School of Medicine in Dallas, has shown that the increase in LDL is not really associated with an increase in apolipoprotein B; therefore the LDL:apoB ratio tends to normalize with therapy. Unless the LDL level begins to get too high, I would not discontinue gemfibrozil. If the reason for treatment was to reduce triglycerides, that in itself would be the major therapeutic benefit.

Question: Is HDL glycosylated as LDL is?

Pr. Norman Miller (Winston-Salem, North Carolina): Yes, in the same way that albumin and many other proteins are, in diabetes. Whether that is significant in terms of its relationship to atherogenesis is not clear. I believe some preliminary data have been presented suggesting that glycoslyated HDL is less able to bind to the cell membranes of cultured cells and to promote the efflux of cholesterol from those cells, but this needs to be confirmed.

Question: Can you offer any information about the use of natural materials, other than alcohol, to increase HDL? We have found that using rapeseed oil from Argentina as a food supplement significantly increases HDL, particularly in persons with relatively low levels of HDL (<40 mg/dl) to begin with.

Dr. Miller: You've touched on an area that certainly deserves exploration. Although we know that diets rich in saturated fats and cholesterol tend to increase HDL in the same way as they increase LDL, we know very little about the effects of other dietary components.

Question: When HDL cholesterol is reduced by an agent such as probucol, what is the mechanism involved? Are the HDL particles or the HDL cholesterol reduced and, if the latter, is the reverse cholesterol transport system implicated? Would that be related to peripheral apo E production and its role in HDL uptake by the liver?

Dr. Miller: This issue is still being investigated. Some interesting preliminary data from Japan suggest that probucol may somehow increase the efflux of cholesterol from cultured cells—from the spleen, I believe—and may also promote the synthesis of apo E. One could hypothesize that an increase in apo E synthesis may increase the clearance of HDL from the circulation. On the other hand, in vivo studies of the turnover of apo AI have shown a decrease in apo AI synthesis, as well as an increase in the fractional catabolic rate of apo AI, although the results were not statistically significant. If we look at the composition of HDL in patients treated with probucol, we find that the percentage of small HDL particles is in-

creased. It's conceivable that the probucol-induced decrease in HDL is not detrimental.

Question: How vigorously should one manage the patient with diabetic hyperlipidemia, given the results of the World Health Organization study on high triglyceride levels in microvascular disease and the NCEP Guidelines about male gender and diabetes being risk factors for CAD?

Dr. Antonio M. Gotto, Jr. (Houston, Texas): I think we should be very vigorous in treating hyperlipidemia in the diabetic patient, whether the problem is an increase in LDL or hypertriglyceridemia with low HDL. At least 2 mechanisms are involved in the development of hyperlipidemia: In severe insulin deficiency, as in diabetic ketoacidosis, a deficiency in lipoprotein lipase leads to a decreased rate of removal of triglyceride remnant particles from the circulation. Second, there is some evidence that hyperinsulinemia may increase VLDL synthesis and cause VLDL and triglyceride levels to increase.

Management should include rigorous control of glucose intolerance with diet, exercise and insulin or an oral hypoglycemic agent. Once this has been achieved, one can consider the various agents available. Gemfibrozil would be the agent of choice for diabetic patients with high triglyceride and low HDL levels. As Dr. Schaefer has pointed out, nicotinic acid interferes with glucose control in the diabetic patient. For the patient who primarily has elevated LDL, a bile acid-binding resin or lovastatin could be used.

Question: Beta blockers are known to have an adverse effect on HDL cholesterol. Is this clinically relevant and are some beta blockers less offensive than others?

Dr. Gotto: We don't yet know the clinical significance. Beta blockers with intrinsic sympathomimetic activity do not appear to increase triglycerides or decrease HDL. In general, if a patient with hypertension also has high total cholesterol or triglyceride levels or a low HDL level, it's prudent to avoid using a drug that will treat one risk factor while exacerbating another.

CONCLUDING REMARKS (Antonio M. Gotto, Jr.)

Certainly there is overwhelming evidence from epidemiologic studies, case-control studies and clinical trials that relates HDL levels and coronary disease. Nevertheless, many questions remain unsolved. Physicians must continue to rely on their best clinical judgment when approaching the patient with lipid disorders, especially with low HDL levels. We do not have ways of increasing HDL without altering other lipoprotein fractions. It is clear that the Helsinki Heart Study, in which gemfibrozil exerted its primary effect on HDL while lowering LDL, has offered additional insight.

In any case, the role of HDL is important, and screening for HDL will be carried out over the next few years as our methods improve. Over time, the National Institutes of Health will review the NCEP Guidelines and determine whether to revise the recommendations concerning HDL measurement or whether the primary focus should continue to be on LDL. In addition, it may become clear that HDL and triglycerides should be included in the equation as targets for therapy and not just be considered additional risk factors for coronary artery disease.

The American American Journal of Cardiology

OCTOBER 2, 1990

A Symposium: Angiotensin-Converting Enzyme Inhibition Therapy in the Treatment of Congestive Heart Failure

GUEST EDITOR:

Jay N. Cohn, MD

Professor of Medicine Head, Cardiovascular Division University of Minnesota Medical School Minneapolis, Minnesota

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Introduction

Jay N. Cohn, MD

ngiotensin-converting enzyme (ACE) inhibitors are gaining popularity as adjuvant therapy in the management of heart failure. The increasing use of ACE inhibitors is based on early clinical studies that demonstrate the hemodynamic effectiveness of the drugs and on intermediate-term clinical trials that demonstrate improvement in symptoms and exercise tolerance. More recently, the demonstration of a striking reduction in mortality in patients with severe class IV heart failure has further stimulated the use of these drugs in patients who remain symptomatic while receiving more conventional treatment. In addition, recent studies appearing to show efficacy in patients with mild heart failure have encouraged some physicians to recommend that these drugs be administered as the agent of first choice for the treatment of this syndrome.

The rapid expansion of clinical indications for the use of ACE inhibitors in patients with heart disease has increased the need for more comprehensive insight by practicing physicians into the mechanisms of action of these drugs, their pharmacokinetics and pharmacodynamics, their interaction with protean neurohormonal mechanisms and their potential effects at the tissue level to alter the natural history of the syndrome of heart failure.

This symposium was designed to address some of the issues that are of importance in understanding how to use ACE inhibitors in patients with heart failure. In my article, I have tried to place the use of ACE inhibitors in the perspective of the disturbed pathophysiology of heart failure. New understanding of the mechanisms in heart failure may lead to a revision of our current concepts of the action of ACE inhibitors.

Dr. Robert Cody reviews the pharmacokinetics and pharmacodynamics of the three ACE inhibitors currently marketed in the United States—captopril, enalapril and lisinopril. An understanding of the differences between these agents is critical for their proper use in heart failure.

Dr. Steven Gottlieb explores the action of ACE inhibitors on the kidney. Not only is the kidney the primary site of origin of renin, but the renal effects of these drugs may be critical to their therapeutic efficacy and toxicity.

Dr. Gary Francis addresses the systemic neurohormonal mechanisms that appear to be activated in heart

failure. The vascular, metabolic and cellular effects of this neurohormonal stimulation may be a key to symptoms and progression of heart failure. Therapeutic approaches, including the use of ACE inhibitors, are dependent on an understanding of these mechanisms.

Dr. Alan Hirsch extends our understanding of neurohormonal responses to the tissue renin-angiotensin system, which may be a key factor in the therapeutic response to ACE inhibition. Although many features of this tissue system are still controversial, there is growing evidence that it plays a role in the heart failure syndrome.

Dr. Karl Swedberg reviews newer data from the CONSENSUS trial describing the relation between the clinical efficacy of enalapril and the neurohormonal response to heart failure. These data support previous evidence that neurohormonal activation is a prognostic marker in heart failure.

The discussions of these papers are presented in this supplement because they help to clarify some practical points pertaining to the treatment of heart failure. The hope is that these papers and the discussions will serve as a state-of-the-art presentation that focuses on what is known and what is yet to be learned about ACE inhibitors for heart failure.



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Mechanisms in Heart Failure and the Role of Angiotensin-Converting Enzyme Inhibition

Jay N. Cohn, MD

The four major diagnostic criteria for the syndrome of congestive heart failure are left ventricular dysfunction, exercise intolerance, pulmonary congestion or edema and ventricular arrhythmias. Activation of norepinephrine, angiotensin II, vasopressin and atrial natriuretic peptide may be a key factor in the vasoconstriction and increased impedance to left ventricular ejection in heart failure. Interventions that interfere with these vasoconstrictor mechanisms should have a salutary effect on left ventricular performance. Treatment with angiotensin-converting enzyme (ACE) inhibitors. α -adrenoceptor blockers and vasopressin antagonists has resulted in hemodynamic benefits, but it has been more difficult to demonstrate long-term clinical effectiveness. Reductions in mortality have been demonstrated in patients with heart failure treated with vasodilators and ACE inhibitors. Improvement in the quality of life and prolongation of life are the only two appropriate goals in the management of heart failure. Further understanding of the role of angiotensin II and its interference by ACE inhibition in the tissue processes of heart failure is needed.

(Am J Cardiol 1990;66:2D-6D)

rowing knowledge about the clinical syndrome of heart failure has led to controversies about its diagnosis and uncertainties as to how the complex pathophysiology contributes to the natural history of the syndrome. One key to the complex pathophysiology of heart failure has been the favorable clinical effects noted in response to treatment with angiotensin-converting enzyme (ACE) inhibitors. Although this was initially accepted as evidence for the efficacy of vasodilator therapy, new understanding of the actions of angiotensin II and of the pharmacologic effects of ACE inhibitors has made even this observation less than simple. To set the stage for the more focused review of the potential mechanisms of action of ACE inhibitors, I shall review in broad terms some of the pertinent clinical and pathophysiologic manifestations of heart failure.

DIAGNOSIS OF HEART FAILURE

Ventricular dysfunction can be quantitated by a number of hemodynamic measurements made either at rest or during exercise or other stresses. This quantitative assessment of ventricular function may provide a precise means of evaluating performance of the heart in physiologic terms. Recent experience, however, has made it clear that considerable ventricular dysfunction may exist in the absence of symptoms, and thus the clinical syndrome cannot accurately be described by such quantitative assessment of pump function. Nonetheless, since heart failure is a syndrome that has its origin in heart muscle dysfunction, demonstration of left ventricular dysfunction should be a sine qua non for the diagnosis.

The chief clinical manifestation of heart failure is reduced exercise capacity because of dyspnea or fatigue. Therefore, the simplest definition of heart failure is that it is a syndrome in which left ventricular dysfunction is accompanied by exercise intolerance. Two other manifestations of the clinical syndrome are so common that they are best included in the primary diagnostic criteria. Sodium retention manifested by pulmonary congestion or peripheral edema is often a hallmark of the disease and has led to use of the term congestive heart failure to describe the syndrome. Although most patients with heart failure do indeed have congestive signs or symptoms, these are not necessary for the diagnosis. Thus, left ventricular dysfunction accompanied by exercise intolerance in the absence of congestion can still be diagnosed as heart failure.

Ventricular arrhythmias, including premature ventricular depolarizations and runs of asymptomatic nonsustained ventricular tachycardia, are also commonly present in the syndrome.² Although not all patients have such ventricular arrhythmias, and their presence is not necessary for the diagnosis of heart failure, their detec-

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tion may best be accepted as a component of the syndrome and not an independent problem that needs specific evaluation. These four major diagnostic criteria for the syndrome of heart failure are shown in Figure 1. The syndrome of clinical heart failure includes all patients with left ventricular dysfunction and exercise intolerance, whereas the diagnosis of congestive heart failure should be confined to patients who also exhibit edema and congestion.

NEUROHORMONAL ACTIVATION IN HEART FAILURE

The relation between the clinical manifestations of heart failure (exercise intolerance, sodium retention and ventricular arrhythmias) and the physiologic impairment in left ventricular function is not simple. A poor correlation between each of these variables suggests that mechanisms other than the simple impairment of ventricular function contribute to these disturbances.3 Neurohormonal activation has been proposed as a key contributor to the syndrome's clinical manifestations and progression. The evidence that these systems are activated in heart failure comes from a variety of studies in patients with the overt clinical syndrome. Activation of the sympathetic nervous system is manifested by elevated circulating plasma norepinephrine levels, 4,5 by elevated norepinephrine spillover rates assessed by kinetic studies using tritiated norepinephrine,⁶ and by increased efferent sympathetic nerve traffic measured from the peroneal nerve in patients with heart failure.7 In recent studies,8 an increase in plasma norepinephrine has also been demonstrated in patients with left ventricular dysfunction who do not have overt signs of heart failure. Thus, the increased activity of the sympathetic nervous system may be a somewhat nonspecific response to impaired left ventricular function.

Activation of the renin-angiotensin system is also common in patients with heart failure. Indeed, some patients exhibit exceedingly high levels of plasma renin activity indicative of intense renal release of renin.⁹ The high levels are particularly common in patients with decompensated heart failure, most of whom are also receiving large doses of diuretics that might contribute to the stimulation of renin release from the kidney. In other patients, however, even some with severe symptoms of chronic congestive heart failure, plasma renin activity may be normal and may exhibit a relatively attenuated response to sodium restriction and to furosemide.¹⁰ The mechanism of this heterogeneity of renin response in patients with heart failure is not known.

Plasma arginine vasopressin and atrial natriuretic peptide levels are also increased in patients with heart failure. Vasopressin levels average about twice the normal level in patients with heart failure. The mechanism of this increase is not known, although it is thought to be largely nonosmotic in origin; the possible role of this vasopressin stimulation in contributing to water retention and hyponatremia remains an attractive hypothesis. Atrial peptide levels increase in response to atrial stretch, and the increase in heart failure appears to correlate with the degree of venous congestion. 13

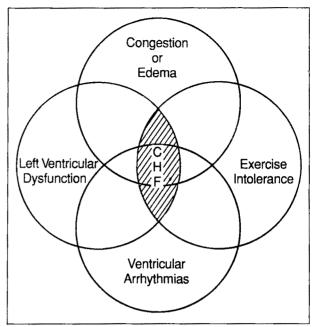


FIGURE 1. The four major diagnostic criteria for the syndrome of congestive heart failure (CHF).

The potential physiologic effects of this neurohormonal stimulation are well known to circulatory physiologists. An increase in vascular resistance and a decrease in vascular compliance are prominent vascular actions of norepinephrine, angiotensin II and vasopressin.¹⁴ Atrial natriuretic peptide may exert vasodilator effects in some vascular beds under certain conditions, but its vasodilator effect appears not to be very potent and may downregulate with chronic stimulation. 15 Thus, the net effect of activation of these four hormonal systems is an increase in vascular tone that raises impedance to left ventricular ejection. Since increased impedance is a critical determinant of left ventricular performance in patients with heart failure, 16 this neurohormonal activation may be a key factor in a progressive deterioration of left ventricular function that may contribute to the natural history of the syndrome. However, other actions of these systems may also be critically involved in the process. The sympathetic nervous system stimulates myocardial contractility through β -receptor effects, but long-term stimulation may result in downregulation of these β receptors and an impaired peak capacity for contractility.¹⁷ Coronary vasoconstrictor effects of all of these hormonal systems may impair myocardial perfusion, particularly to the subendocardium, and may add a metabolic component to the ventricular dysfunction even in patients without ischemic heart disease. 18 The renal vasoconstrictor and intrarenal effects of these hormones may contribute to sodium retention, water retention and congestive symptoms in heart failure. 19 Furthermore, the adrenal stimulatory effect of angiotensin II contributes to hyperaldosteronism in heart failure and thus to hypokalemia, which may aggravate the metabolic abnormality.²⁰ A recently recognized effect of angiotensin II is its direct effect on cellular growth. Both vascular and cardiac tissue may respond

to this hormone by hyperplasia or hypertrophy, 21-23 which could be a key to the progressive changes in ventricular function and progressive changes in vascular impedance that contribute to the natural history of the syndrome.

PHARMACOLOGIC INTERVENTION IN HEART FAILURE

If these neurchormonal mechanisms are key to the vasoconstriction and increased impedance in heart failure, interventions that interfere with these vasoconstrictor mechanisms should have a salutary effect on lefventricular performance. This has certainly been the case with short-term administration of α -adrenoceptor blockers,²⁴ ACE inhibitors^{25,26} and vasopressin antagonists.²⁷ The problem in the last decade has not been to demonstrate a favorable hemodynamic effect of the administration of these drugs, but to demonstrate that this hemodynamic benefit can be translated into a long-term clinical response. Variable effects have been noted in previous trials in terms of the four major clinical manifestations of heart failure. Although an acute increase in cardiac output and decline in left ventricular filling pressure are hallmark: of the response to vasodilator drugs,28 long-term improvement of left ventricular performance as manifested by a reduction in heart size or an increase in ejection fraction has been more difficult to demonstrate. In some of the ACE inhibitor trials²⁹ and in the Veterans Administration Cooperative Study (V-HeFT),30 which used hydralazine and isosorbide dinitrate therapy, a modest increase in ejection fraction could be demonstrated. Exercise tolerance has been difficult to quantitate because of the variabilities in protocol design and end points used in different studies. In some trials, particularly those of ACE inhibitors, an increase in peak exercise performance has been demonstrated.^{29,31,32}

Relief of congestion and edema would be clear manifestations of an in-provement in the clinical syndrome of heart failure, but the use of diuretics in most clinical trials has clouded this evaluation. In most patients, diuretic therapy has continued to be required despite the administration of effective vasodilator or neurohormonal-inhibiting agents. Although ventricular premature beats are a common manifestation of the syndrome of heart failure, it is not yet clear whether their inhibition should be considered a favorable effect.33 In most trials, it has been difficult to demonstrate that treatment has had a favorable effect on the frequency of premature beats, although some³² have demonstrated a reduction in premature beats in response to ACE inhibitors.

Effects on mortality, which is a more definitive end point, have been demonstrated in two controlled trials. In V-HeFT,³⁰ the group treated with hydralazine and isosorbide dinitrate in addition to digoxin and a diuretic demonstrated a lower mortality than patients given placebo in addition to digoxin and a diuretic. The reduction in mortality appeared to demonstrate for the first time that the natural history of the syndrome could be favorably influenced by interference with the vasoconstrictor mechanisms present in the disease. The CONSENSUS trial³⁴

in northern Scandinavia of patients with more severe heart failure demonstrated a remarkable reduction in 6and 12-month mortality in patients given enalapril compared with those given placebo in addition to more traditional therapy.

These two studies have been interpreted as showing the potential efficacy of an effective vasodilator regimen in patients with heart failure. Comparing these studies is somewhat hazardous, however, because the patient populations were so different and the treatments were not identical. Nonetheless, at 1 year after randomizationthe only interval that could be directly compared in these two trials—the magnitudes of the reductions in mortality were similar. Thus, one interpretation of these findings is that both regimens reduced the impedance to left ventricular ejection that was contributing to the increased mortality and that either drug could be used to produce a favorable effect. An alternate hypothesis, however, is that the drugs actually act by different mechanisms and that the vasodilator effect of the hydralazine and isosorbide dinitrate is quite different from the overall cardiovascular effect of the ACE inhibitor and that the 2 interventions might even be additive in their effect if they had been studied in that way. The V-HeFT II trial is now comparing enalapril and hydralazine-isosorbide dinitrate therapy in patients with mild to moderate heart failure. An appropriate future study might be the comparison of either one of these agents with the other added to it in order to assess their combined efficacy.

MECHANISM OF DEATH

The mechanism of death in patients with heart failure has been no less controversial than the pathophysiology of the syndrome. Sudden, apparently instantaneous death is a common occurrence in patients with heart failure and is usually attributed to a lethal ventricular arrhythmia. Although this is probably true in many cases, recent documentation³⁵ of the frequent occurrence of electromechanical dissociation in the absence of arrhythmias as a cause of instantaneous death has raised some concern about the mechanism in these patients. The mechanisms of death in the V-HeFT and CONSENSUS trials appeared to be different. In V-HeFT, 44% of the deaths were reported as occurring suddenly in the setting of clinical stability, with arrhythmia as a likely cause. In CONSENSUS, the frequency of sudden death was lower. probably because the patients had both severe heart failure and severe pump dysfunction that most often manifested itself as pump failure.

Thus, the CONSENSUS trial could demonstrate no reduction in the occurrence of sudden death in response to enalapril, whereas V-HeFT demonstrated a reduction in sudden death as well as pump failure death with hydralazine-isosorbide dinitrate treatment. The classification of mechanisms of death in heart failure and the potential differential effect of various treatments on the mechanism of death will probably remain controversial until the classification system is more universally applied and until more data can be obtained on rhythms recorded at the time of apparent sudden death.

GOALS OF TREATMENT

There are only two appropriate goals in the management of patients with heart failure: improvement in the quality of life and prolongation of life. The other end points often used in clinical trials can only serve as surrogates for the two major treatment goals. Although such quantitative measurements as hemodynamics and peak exercise performance are often used as surrogates for quality of life, it is apparent that in long-term efficacy studies these may not provide an adequate assessment of the patient's state of well-being. Self-assessment questionnaires that address questions directly related to the heart failure syndrome may be more appropriate, but they are not yet adequately validated as indices of the quality of life.³⁶⁻³⁸ Much effort has been expended on identifying factors that contribute to the risk of mortality in heart failure, and we may be approaching the time when surrogates for mortality might be available. In the meantime, however, there appears to be no substitute for the measurement of the effect of treatment on mortality to assess its capacity to alter the natural history of the

The natural history of the syndrome of heart failure is now a primary focus of interest in worldwide investigations. It is apparent that the syndrome may progress in the absence of new insults to the myocardium related to the etiology of the heart disease. The role of neurohormonal and other mechanisms in contributing to the hypertrophy and dilation of the left ventricle and the hypertrophy and constriction of the peripheral vasculature may be critical components in the progression. New insights into the role of angiotensin II and its interference by ACE inhibition in these tissue processes are urgently needed. As this new information accumulates, it may be possible to expand our understanding of the role of ACE inhibition on both the circulating and the tissue renin-angiotensin system. Other new agents will be developed that may interfere at different points in the renin-angiotensin cascade and in the other systems that control vascular tone and myocardial growth. In the meantime, however, physicians have been provided with powerful pharmacologic tools to interfere with the symptomatology and probably the mortality in this complex clinical syndrome. In the other contributions to this symposium, we shall explore the present state of knowledge and future directions for our study of ACE inhibitors.

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DISCUSSION

- Dr. Stephen Gottlieb (Baltimore, Maryland): In patients with heart failure whom I follow, I find it difficult to determine which patients die suddenly. It seems to me that it is impossible in a multicenter study. Furthermore, there is a recent report that sudden death, which appears to be secondary to ventricular arrhythmias, often is not. Do our arbitrary definitions really reflect the mechanism of death?
- Dr. Jay Cohn (Minneapolis, Minnesota): Certainly, the fact that patients may die suddenly with a normal sinus rhythm throughout the terminal episode has been well established. It is not uncommon for acute electromechanical dissociation to be a terminal event in patients with severe heart failure. But the general feeling is that, although lethal bradyarrhythmias and electromechanical dissociation do occur, ventricular fibrillation is probably more common. We do, of course, run the risk of including these bradyarrhythmias and electromechanical dissociations in the sudden death group. Dr. Swedberg, do you want to comment on this?
- Dr. Karl Swedberg (Gothenburg, Sweden): Among the 118 patients who died in our study, most of the patients who had a cardiac death died because of progression of heart failure. However, when we studied the type of arrhythmias ir. these patients, the arrhythmias were very complex. Accordingly, the arrhythmias express the myocardial disease. I also think it is unwise to extrapolate the findings from these patients to those with milder forms of heart failure.
- **Dr. Cohn:** How confident are you that it was a progression of heart failure and not sudden death in the presence of heart failure?
- **Dr. Swedberg:** I am quite confident, because there were patients who had improved and had left the hospital in most cases. For example, one patient had a clear improvement but was found dead in the hospital lobby when leaving for home.
- **Dr. Alan Hirsch (Boston, Massachusetts):** Dr. Cohn, you have discussed the importance of the sympathetic

- nervous system and the renin-angiotensin system in heart failure pathophysiology. If sudden death reduction is an important end point, can the efficacy of a pharmacologic intervention be judged by its effect on the pretreatment predictors of mortality? In other words, can treatment with hydralazine and a nitrate lower plasma catecholamine levels in a manner predictive of improved survival? Alternatively, does the magnitude by which ACE inhibitors lower plasma angiotensin II concentrations predict improvement in the sudden death rate in any population studied?
- **Dr. Cohn:** There is as yet no data adequate to address the effect on survival of a drug-induced change in predictors of survival.
- **Dr. Swedberg:** We made up a prediction score based on the combined neuroendocrine activation, and it is clear that patients who had neuroendocrine activation died as a result of the progression of heart failure.
- **Dr. Cohn:** Our original data that the very high norepinephrine levels were a predictor of progressive pump failure death, not of sudden death, would fit in with Dr. Swedberg's data. In fact, among the patients with normal or modestly elevated norepinephrine levels who died, it was more commonly sudden death. So there is no support from the data that the sympathetic nervous system is an important factor in sudden death, whereas it certainly is a marker for, or a risk factor in, pump failure death. Of course, the limiting factor in all these studies is that we do not have the luxury of obtaining hormonal measurements at the time the patient dies.
- Dr. Gary Francis (Minneapolis, Minnesota): We have recently reviewed some retrospective data on norepinephrine; because they are retrospective, they are not particularly strong. We also found that patients who tended to have a progressive rise in norepinephrine over time are more likely to die of progressive pump failure, whereas patients who died suddenly tended to have a relative lack of increase in plasma norepinephrine over time.
- **Participant:** We should consider other neurohormones as well; angiotensin II itself might be directly arrhythmogenic.
- **Dr. Francis:** What we found with renin, not angiotensin II, was that renin levels seem to reflect the clinical status of the patient. When patients experience decompensation, renin levels rise sharply, and when they are better, the renin levels decrease.
- the Veterans Administration Cooperative Study (V-HeFT) results is that patients who are going to die suddenly do so most often within the first year after the diagnosis and start of treatment and that the risk of sudden death decreases with time. Of course, the risk of pump failure death increases with time. If the patient has not had a ventricular arrhythmia for a year, he or she is unlikely to have the substrate for ventricular fibrillation, whereas pump failure is a progressive pattern. I am not sure how to incorporate that into our management scheme, but it may be an important observation.

Pharmacology of Angiotensin-Converting Enzyme Inhibitors as a Guide to Their Use in Congestive Heart Failure

Robert J. Cody, MD

The pharmacokinetics of the angiotensin-converting enzyme (ACE) inhibitors are difficult to assess for several reasons. First, these compounds exert their influence by inhibiting an intermediary enzyme of a cascade of enzymatic events, whose ratelimiting enzyme (renin) is not directly affected by ACE inhibition. Second, renin and angiotensin I accumulate during ACE inhibition and a change in the dose of an ACE inhibitor could produce sudden shifts of angiotensin I to angiotensin II. Third, components of the circulating renin system require the interaction of several organ systems and effector sites. Fourth, the kinetics of ACE inhibitors can be influenced by the organ systems responsible for drug absorption, metabolism and excretion, and the functional status of these systems can be affected by the heart failure process. Fifth, at least some portion of the cardiovascular effects of ACE inhibitors is influenced by the contributions of other systems whose physiologic effects may be of importance in some patients with congestive heart failure. Sixth, the potential impact of tissue-bound ACE is not yet fully understood. Finally, for appropriate drug dosing, the effects of aging on the heart failure process, the extent of renin system activity. and the disposition of ACE inhibitors need to be considered. Because of their complex pharmacokinetics, treatment with ACE inhibitors has been guided by their pharmacodynamic and clinical characteristics.

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The renin-angiotensin-aldosterone system is an important hormonal pathway in congestive heart failure (CHF)1 because it produces excessive arterial vasoconstriction and sodium retention. The introduction of angiotensin-converting enzyme (ACE) inhibitors. the activity of which blocks angiotensin II-mediated vasoconstriction and aldosterone-mediated sodium retention, is an important advance in the treatment of CHF. Considerable data on the clinical efficacy of these drugs have been accumulated, but less is known about their pharmacokinetics and pharmacodynamics. The results of pharmacokinetic studies have been reviewed. 2-5 As reported in this article, the effects of aging and progressive renal dysfunction in patients with CHF may be particularly relevant to treatment with ACE inhibitors. Clinical pharmacodynamics and the outcome of physiologic studies and clinical trials provide a good guideline for ACE inhibitor dosage and utilization.

THE RENIN-ANGIOTENSIN SYSTEM

Angiotensinogen, a serum α_2 -globulin, is produced by the liver and circulates in plasma as a biologically inactive peptide. Renin is a proteolytic enzyme secreted by the juxtaglomerular apparatus of the kidney that cleaves 4 amino acids from angiotensinogen to form the decapeptide angiotensin I, which also has minimal vasoactive properties. Many factors contribute to the secretion of renin; the three most important involve sympathetic nervous system activation, baroreceptor regulation of afferent renal arterial tone and reduction of distal tubular sodium delivery to the macula densa. Once secreted, renin cleaves 4 amino acids from angiotensinogen to form angiotensin I. This enzymatic process is the rate-limiting step of the renin-angiotensin system cascade. Angiotensin I is converted to the octapeptide angiotensin II with the removal of 2 more amino acids by the dipeptidyl carboxypeptidase converting enzyme. It was long believed that this conversion occurred primarily in pulmonary tissue, but tissue-bound converting enzyme has been found throughout the body, most notably in vascular and myocardial tissues. The end product, angiotensin II, is a potent vasoconstrictor.

Angiotensin II is also a potent stimulus for aldosterone secretion from the adrenal cortex. The hormonal actions of aldosterone include distal tubular sodium reabsorption and potassium excretion. Because the radioimmunoassays for angiotensin I and angiotensin II are technically difficult, the most useful and readily available measure of activity of the renin-angiotensin system is the level of renin. This is assessed by a sensitive radioimmunoassay that measures the conversion of angiotensinogen

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to angiotensin I and is expressed as plasma renin activity. Increased secretion of renin has been found in most CHF patients. Despite newer concepts about the potential role of tissue renin systems, the endocrine-renin system is clearly abnormal in many patients with CHF.

CAPTOPRIL IN HEALTHY SUBJECTS

The pharmacokinetics of captopril have been previously outlined.^{2,3} Captopril is rapidly absorbed from the gastrointestinal tract in healthy subjects; levels are detectable as early as 15 minutes after administration About 60 to 75% of an oral dose of captopril is absorbed, consumption of food will decrease absorption by 30 to 40%. It is not known whether captopril crosses the placenta; it is not readily secreted into human breast milk. Captopril is 25 to 30% protein bound, and the volume of distribution of unchanged captopril (10 mg) at steady state was 0.7 ± 0.04 L/kg. Once absorbed, captopril is metabolized to several forms, including a disulfide dimer of captopril. a captopril-cysteine disulfide and other mixed disulfides with endogenous thiol compounds. Cartopril and its pool of metabolites probably undergo reversible interconversions.

Captopril and its metabolites are primarily excreted by the kidneys, with a minor role for elimination in the feces, which may represent unabsorbed captopril. The primary mechanism of renal excretion is tubular secretion, accounting for 78% of urinary captopril. The elimination half-life of unchanged captopril is about 1.7 hours. correlating closely with measurements of renal function. The concomitant administration of probenecid to subjects receiving constant intravenous infusions of captop-il reduced renal clearance by 44% and total body clearance of captopril by 19%. Marked increases in elimination half-life to more than 20 to 40 hours have been reported in patients with reductions of creatinine clearances to less than 20 ml/min. Thus, doses of captopril should be cecreased accordingly in patients with renal dysfunction, which is present in many patients with CHF.^{6,7}

CAPTOPRIL IN CONGESTIVE HEART FAILURE

Single-dose pharmacokinetics were studied in 12 patients with chronic CHF who were given a single oral dose of 25 mg of captopril in the fasting state.8 The peak blood concentration of unchanged captopril (C_{max}) was 122 \pm 16 ng/ml, with a time to peak concentration (T_{max}) of 1.43 ± 0.19 hours. The area under the time-concentration curve for an 8-hour observation period was 249 ng/ml-h. The elimination half-life was 1.06 hours. These pharmacokinetics are similar to those observed in healthy subjects and in hypertensive patients, except for a slightly delayed T_{max}. To assess the effects of short-term cumulative dosing, the pharmacokinetics were reassessed after 5 consecutive days during which 25 mg of captopril was given every 8 hours. The overall pharmacokinetic of unchanged captopril were the same on day 5, with similar C_{max}, area under the curve and elimination half-life. The only difference was a slightly shorter T_{max}. Levels of total captopril (unchanged captopril and metabolic pool) on day I were significantly higher than unchanged captopril levels; furthermore, total captopril concentrations at all time intervals were greater on day 5 than on day 1.

ENALAPRIL AND ENALAPRILAT IN HEALTHY SUBJECTS

Data concerning the pharmacokinetics of the prodrug enalapril (MK-421) and its metabolite enalaprilat (MK-422) are much more limited.^{3,4} Enalaprilat is the active form of the drug, and has potent and prompt activity as an ACE inhibitor when given intravenously, but it is poorly absorbed from the gastrointestinal tract (less than 10%). To increase gastrointestinal absorption, enalapril was modified into a monoethyl ester form. Enalapril is rapidly absorbed in human subjects, with a minimal absorption rate of 60 to 70%, and promptly inhibits angiotensin II formation. In contrast to captopril, the presence of food in the gastrointestinal tract does not appear to influence its absorption. After a 10-mg dose, the C_{max} of enalapril was 140 ± 52 nM (range, 77 to 232 nM) with a T_{max} of 1.0 \pm 0.3 hours (range, 0.5 to 1.5 hours). The area under the curve for 72 hours was 198 \pm 26 nmol/L⁻¹. h⁻¹. Once absorbed, enalapril is rapidly metabolized to its active form, enalaprilat. Thus, intact enalapril is found in the serum for a short period and is almost undetectable 4 hours after oral administration.

In contrast, the distribution of enalaprilat is more prolonged. After 10 mg of oral enalapril, the C_{max} of enalaprilat was 116 ± 50 nM (range, 54 to 220 nM), with a delayed T_{max} of 4.0 \pm 1.5 hours (range, 2 to 8 hours). The area under the curve over 72 hours was 1,409 \pm 437 nmol/ $L^{-1} \cdot h^{-1}$ (range, 750 to 2,121 nmol/ $L^{-1} \cdot h^{-1}$). There was a prolonged terminal phase, with enalaprilat still detectable 96 hours after dosing, in contrast to the short duration of enalapril.

This research^{3,4} also found an effect of aging on enalapril pharmacokinetics: the area under the curve was greater in elderly than in young healthy subjects. The effects of different doses of enalapril (ranging from 1.25 to 20 mg) on the physiologic responses of 20 healthy male subjects were also studied. A dose-dependent response was revealed, with the lowest dose of 1.25 mg having the least effect on blood pressure and plasma renin activity. However, a clear plateau was reached, such that only small differences were noted between the responses to 10 and 20 mg of enalapril. This plateau effect suggested that the plasma drug levels after 10 and 20 mg were sufficient to block ACE activity completely. The de-esterification of enalapril absorbed by the gastrointestinal tract to the active form of enalaprilat occurs primarily in the liver. This postabsorptive hydrolysis can occur in the mucosal lining of the gastrointestinal tract, but this has not been confirmed. In contrast to the multiple metabolites of captopril, there appear to be no major metabolites of enalapril other than enalaprilat. Excretion of enalapril and enalaprilat, like captopril, is primarily renal; therefore, in subjects who have decreased renal function, excretion is delayed.

ENALAPRIL AND ENALAPRILAT IN CONGESTIVE HEART FAILURE

Schwartz et al⁹ gave 8 patients with CHF 5 or 10 mg

of oral enalapril and found major differences in drug pharmacokinetics from those in hypertensive patients. The T_{max} of enalaprilat was normal (5 hours), but the half-life was longer (7 to 8 hours), and enalapril clearance was much slower (0.6 to 0.7 L/min) than in patients with mild hypertension (2.5 to 2.7 L/min). Thus, the longer half-life of enalapril (in its active form, enalaprilat) coupled with a slower clearance could result in a longer duration of action in patients with CHF, indicating the need for a dose reduction or an increase in the dosing interval.⁴

LISINOPRIL IN HEALTHY SUBJECTS

Lisinopril is a lysine derivative of enalaprilat.^{5,10} The active form of lisinopril constitutes the oral formulation; that is, lisinopril does not have to undergo the hepatic deesterification step necessary for enalapril. The time to peak effect of lisinopril is approximately 6 to 8 hours, similar to that of enalaprilat after its conversion from the parent form. Bioavailability is 25 to 50%^{5,10} and is not affected by the simultaneous consumption of food. Lisinopril absorption is not affected by age and it is not significantly bound by plasma proteins. Aging, however, does affect the serum concentration of lisinopril.¹⁰ After a single dose of 20 mg, serum lisinopril levels were 2 to 3 times higher in elderly subjects than in young subjects. Since absorption is not affected by age, this aging effect suggests differences in elimination.

Little, if any, metabolism of lisinopril occurs after its absorption, and virtually all of the absorbed compound is excreted unchanged in the urine. Most of the compound is eliminated in an early phase, while the remainder is excreted during a terminal phase with a half-life of 30 hours. The latter most likely represents saturable binding to ACE. Thus, the elimination half-life in healthy subjects is 12 to 14 hours. Steady-state levels are present within 2 to 3 days, depending on the schedule of administration. In patients with renal dysfunction, serum lisinopril levels are increased and the excretion rate is reduced, 5 thereby prolonging the duration of effect.

LISINOPRIL IN CONGESTIVE HEART FAILURE

The bioavailability of lisinopril in patients with CHF was 16% (range, 8 to 29%), 11 whereas reports in normal subjects indicate a bioavailability of 25%. 10 Since lisinopril is not metabolized to any great degree, these findings indicate decreased renal clearance of lisinopril in CHF. Lisinopril clearance is correlated with creatinine clearance, indicating that patients with reduced creatinine clearance will have a proportional decrease in lisinopril clearance. There is some evidence to suggest that the presence of severe renal impairment may result in drug accumulation, so that dosing must be carefully controlled in patients with CHF in whom there is evidence of decreased renal function.

PHARMACODYNAMICS OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

The pharmacokinetics of ACE inhibitors parallel their effects on hemodynamics and the renin-angiotensin

system, suggesting that the mechanism of action of these agents is through the reduction of angiotensin II-mediated vasoconstriction and inhibition of aldosterone secretion. Unlike other classes of cardiovascular drugs, the mechanism of action of ACE inhibitors does not permit a direct comparison between blood levels and drug effects.

The hemodynamic effects of captopril in patients with CHF are similar to those in hypertensive patients. 12 At peak effect, systemic vascular resistance and arterial pressure are significantly reduced. In contrast to patients with hypertension, however, in patients with CHF, mean pulmonary artery pressure, pulmonary-capillary wedge pressure and right atrial pressure are also reduced significantly after administration of captopril. Because of the dependence of cardiac output on afterload in CHF, the reduction in systemic vascular resistance is associated with a secondary increase in cardiac output. The effects on heart rate have been somewhat variable; in most studies, heart rate remained unchanged, whereas other studies have shown an overall reduction in heart rate in response to captopril. The mechanisms of this effect are unknown.

The hemodynamic effects of enalapril and captopril in CHF patients are similar, ¹²⁻¹⁴ the major difference being the prolonged time course of enalapril. The time to peak hemodynamic effect of enalapril, as manifested by reductions in afterload and systemic vascular resistance and an increase in cardiac output, has ranged from 4 to 24 hours, ^{3,4} and thus it has not been possible to determine the entire duration of action in clinical studies of patients with severe CHF.

The effects of intravenous enalaprilat have been studied in patients with CHF.¹⁵ Nine patients with severe CHF were given 0.625 or 1.25 mg of enalaprilat. After the first bolus injection, peak effect occurred at 30 minutes and plasma renin activity increased from a baseline of 16.8 ± 6 to 86.6 ± 23 ng/ml·h, accompanied by a progressive decrease in circulating plasma aldosterone levels. Immediate hemodynamic changes were also noted, with a peak effect at 30 minutes. There were marked reductions in systemic vascular resistance, mean arterial pressure, right atrial pressure and pulmonary wedge pressure and significant increases in the cardiac index and stroke volume index. No cumulative hemodynamic or neurohormonal changes were noted after a second injection of enalaprilat. Angiotensin II levels decreased from 68 ± 12 to 19 ± 6 ng/ml after the first dose and remained low for 90 minutes. No further reductions in angiotensin II levels were found after the second injection of enalaprilat was given.

Clinical studies thus far demonstrate that lisinopril produces a favorable hemodynamic profile, similar to those noted after other ACE inhibitors.^{5,9-11} As the lysine derivative of enalapril, it can be ingested in an active form. The pharmacodynamics of lisinopril in patients with CHF mirror the clinical and hemodynamic effects of enalaprilat, the active metabolite of enalapril. The longer duration of action of lisinopril results in clinical and hemodynamic differences that parallel the differences in their pharmacokinetics.

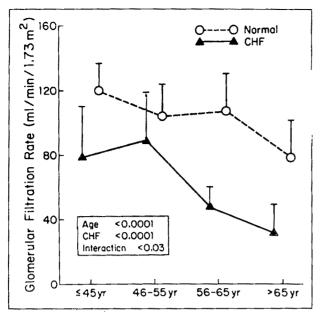


FIGURE 1. Age-related differences of glomerular filtration rate in normal subjects and patients with congestive heart failure (CHF). Although each group demonstrates age-related decline of glomerular filtration rate, the effect is most pronounced in patients with CHF, resulting in a difference between the groups of p <0.03. Data from Cody et al⁶ and Cocy et al.7

USE OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS IN CONGESTIVE HEAFT FAILURE

A review of the pharmacokinetic studies of all ACE inhibitors identifies two factors that are germane to their use in CHF and helps to explain observations from clinical trials. First, aging significantly increases serum levels of ACE inhibitors. Since most patients with CHF are elderly, the aging effect on pharmacokinetics in healthy subjects should not be minimized. Despite the range of physiologic abnormalities produced by CHF, cross-sectional studies reveal an aging profile in CHF patients that parallels that in healthy subjects.6,7 Thus, the dose of ACE inhibitors for elderly (>65 years) CHF patients should be reduced. This aging effect is probably multilactorial, but a major contributor is the reduction in renal function of elderly patients with CHF (Figure 1).6,7 Pharmacokinetic studies of ACE inhibitors repeatedly demonstrate that severe chronic renal insufficiency is associated with increased serum drug concentrations. Since all ACE inhibitors are primarily excreted by the kidneys, this increase of serum drug concentrations is not unexpected. From a pragmatic standpoint, it is not apparent whether this relationship should be considered in choosing a dose of an ACE inhibitor for the treatment of CHF patients. In general, the renal insufficiency of ambulatory CHF does not approach a level of severe chronic renal insufficiency (creatinine clearance <20 ml/min). Nonetheless, many CHF patients, particularly elderly patients, show a creatinine clearance in the range of 40 to 70 ml/min, ^{5,7} so that particular attention to dose may be necessary ir this group.

The conclusion to be drawn from the results of these pharmacokinetic studies is that the pretreatment renal function should be considered when choosing the initial dose of an ACE inhibitor, particularly in elderly patients with heart failure. Since the introduction of ACE inhibitors, observations in clinical trials have fostered a reduction in ACE inhibitor doses. For example, the initial efficacy studies of captopril were conducted with doses of 50 to 100 mg every 8 hours.^{2,12} In clinical practice, the dose likely to achieve a favorable effect is 12.5 to 25 mg every 8 hours. Similar observations have come from trials with enalapril. In initial studies, 13 oral enalapril was effective in a dose range of 2.5, 5 or 10 mg given twice daily. Additional studies summarized e sewhere 12 were consistent with the initial observations. However, when larger doses of enalapril were given, clinically important abnormalities were identified. 16,17 In the early stages of the CONSENSUS trial, 16 unacceptable hypotension was observed with the maximal dosage of 20 mg twice daily (40 mg/day). This prompted a reduction of the maximal dose to 20 mg/day. In fact, since most patients in this trial were elderly, it was subsequently shown that about 20% of patients had clinical improvement with a dose of 5 mg/ day. Administration of 20 mg of enalapril twice a day in patients with severe CHF and prerenal azotemia, who were receiving large fixed doses of diuretics, produced progressive renal insufficiency. These data suggest that an appropriate dose of enalapril is 2.5 to 10 mg given twice daily, with a reduction of dosage or dosage interval in the presence of renal insufficiency. The results of pharmacokinetic and clinical studies indicate that once-daily dosing may be warranted in older patients with impaired renal function or patients with co-existent hypertension. Since enalapril's peak effect occurs 4 to 6 hours after dosing, it should perhaps be administered in the evening, so that its peak effect and blood pressure reduction occur during sleep.

These considerations apply equally, and perhaps with greater emphasis, to lisinopril. However, guidelines for administration of lisinopril in patients with CHF cannot

TABLE I Assessment of the Response to Angiotensin Converting Enzyme (ACE) Inhibition in Congestive Heart Failure

Assessment of the initial response to an ACE inhibitor Measurement of blood pressure Reactive increase of plasma renin activity Symptomatic or clinical response Assessment of the long-term response to an ACE inhibitor Measurement of blood pressure Symptomatic or clinical response Correction of metabolic abnormalities Normalize serum sodium Reduce plasma catecholamines Suppression of renin system activity Reactive increase of plasma renin Suppression of ACE activity Suppression of plasma or urinary aldosterone Excessive ACE inhibitor dosage Symptomatic hypotension Progressive renal azotemia Low-output state or worsening symptoms

be provided at this time, as this indication has not been approved by the Food and Drug Administration.

COMPARISONS OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

The results of some clinical trials have prompted a few clinicians to claim fundamental differences between ACE inhibitors, but there is little convincing data to support these speculations. It is more likely that compounds that block the renin system at other sites (renin inhibitory peptides, angiotensin II antagonists)¹² would have effects that were fundamentally different from those of ACE inhibitors. This is emphasized by the fact that ACE is a carboxypeptidase with additional biochemical activities. In clinical trials, it is virtually impossible to control for all variables that may affect outcome in direct comparisons of ACE inhibitors, and it is even more difficult to compare the results of 1 ACE inhibitor in 1 trial with the results of a second ACE inhibitor in another trial. There are major differences in the pharmacokinetics of ACE inhibitors. These include onset and duration of effect, the need for metabolic activation (enalapril). activity and accumulation of metabolites (captopril) and the potential for drug accumulation in the presence of renal failure (all ACE inhibitors to varying degrees).

ANGIOTENSIN-CONVERTING ENZYME INHIBITOR DOSAGE GUIDELINES

The outcomes of clinical trials suggest that the best pharmacodynamic measure of ACE inhibitors in CHF is the single patient bioassay. When therapy is initiated, particular attention to factors that influence clinical outcome, such as age, magnitude of blood pressure reduction and baseline renal status, will yield the best pharmacologic results with ACE inhibition. Factors used to assess responses to ACE inhibition in patients with CHF are outlined in Table I.

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DISCUSSION

The Aging Effect

Dr. Gray Francis (Minneapolis, Minnesota): Dr. Cody, your observation that the filtration fraction tended to decrease with age in patients with heart failure was very interesting. It could be that the mesangium contracted with a resultant change in the $K_{\rm f}$ or surface area; that could also account for a reduction in the filtration fraction. My understanding is that the sympathetic nervous system does not have a primary action on the afferent arteriole, which is primarily under prostaglandin control. The decrease in filtration fraction may well be due to the effects of angiotensin II on mesangial contraction.

Dr. Robert Cody (Columbus, Ohio): The point I wanted to make was that the action of angiotensin-converting enzyme (ACE) inhibitors on efferent vasoconstriction is not the only process that is going on. To emphasize that point, I have always looked to the other side of the glomerulus. The mesangium can contract, but to what extent norepinephrine simultaneously influences afferent, efferent or mesangial vascular tone can only be estimated from a composite portrait of multiple lines of research. Norepinephrine seems to have a more ubiquitous effect on arteriole tone in the kidney than does angiotensin II.

Participant: Dr. Çody, since plasma renin activity decreases with age, does this mean that the renin-angiotensin system also becomes less important?

Dr. Cody: More and more studies are showing that activity of the renin-angiotensin system decreases with age in normal subjects, which implies that it does become less important. But it is not known whether this decrease is relevant only to circulating levels. In examining all our data on the aging effect in heart failure, we found that catecholamine levels increase with age in patients with heart failure, just as they do in persons without heart failure, even though baseline levels are higher. The renin system activity did not show as much of an age-related decline in patients with heart failure as would have been expected.

Dr. Jay Cohn (Minneapolis, Minnesota): I wonder whether a reduction of the renin system with age is a manifestation of the rise in blood pressure with age. Of course, heart failure provides another stimulus for the renin-angiotensin system that may counterbalance the effect of age.

The slope of renal blood flow with age in healthy persons is exactly the slope we see in vascular compliance with aging. Vascular compliance seems to decrease with age at about the same rate that renal blood flow decreases, which suggests that this may be a vascular aging phenomenon. Initially, the effect of heart failure on vascular compliance seems to be an active process, rather than an aging process. The 2 processes probably produce rather similar changes, until aging eventually takes over.

Dr. Karl Swedberg (Gothenburg, Sweden): I would also like to comment on the age factor. In the CONSEN-SUS trial, the mean age of the study participants was 7) years, which is probably why we had some initial protlems with the drug dosage. In the final analysis, we found that 20.4% of the patients in the enalapril group were treated with 5 mg or less a day. The study was not designed to determine the optimal dose, but it is important to realize that we used a small dose in a larger number of

Dr. Cohn: The CONSENSUS population was so much older than any other group of heart failure patients enrolled in clinical trials that the results raise many questions about what would happen in a younger population.

Dr. Cody: Some fascinating aging changes have been found within the glomerular tuft. Glomeruli develop that have no mesangium; it is in essence a direct shunt between the afferent and the efferent glomerular arterioles.

Effect of Angiotensin-Converting Enzyme Inhibitors

Dr. Alan Hirsch (Boston, Massachusetts): Dr. Cocy, you discussed several factors that can affect the efficacy of an ACE inhibitor; I would like to discuss 2 more. First, disease states have been shown to alter the pretreatment ACE activity of target tissues, so a greater tissue conc∈ntration of the drug may be required. Second, long-term ACE inhibition itself may modulate ACE levels, so that plasma ACE activity may double or triple with long-te-m treatment.

You seemed to downplay the role of efferent arterio.ar constriction. I was also intrigued by the changes that you discussed regarding the filtration fraction decline with aging. Although the filtration fraction is a derived index. which obviously takes into account both intrarenal hemodynamic and glomerular parameters, efferent artericlar tone is probably still a most important contributor.

Dr. Cody: I am not suggesting that the efferent arteriole has no role in controlling the filtration rate. What I am trying to emphasize is the fact that the other important vascular control sites within the kidney appear to have been neglected in congestive heart failure, in deference to the role of efferent vasoconstriction. If you think of every slide you have ever seen about the kidney in heart failure or in hypertension and the effects of ACE inhibitors, they all show angiotensin II clamping the efferent arteriole, and that is the end of the story. It is not that simple.

Dr. Cohn: In reactive hyperreninemia, the system is obviously being suppressed, and there is a feedback loop. Dr. Cody, you have used that as one of your guideposts to adequacy of ACE inhibition. Does that hyperreninemia persist? If it does not, why not? Are there implications for

the rise in angiotensin I levels that will clearly occur when conversion is inhibited?

Dr. Cody: Initially at least, reactive hyperreninemia was used primarily in hypertensive patients as an assessment of response, particularly in renovascular hypertension. Reactive hyperreninemia has been the basis for what Dr. Laragh and others have now popularized as the captopril test for renovascular hypertension. If there is evidence of renal artery stenosis, renovascular hypertension is not identified primarily by the magnitude of blood pressure reduction in response to an ACE inhibitor, but by the magnitude of the renin increase. In a patient who has been taking an ACE inhibitor for 2 months, whose baseline renin level was 20 ng/ml/hr and is now 40 ng/ ml/hr, it can be presumed that he or she is probably taking the drug and it is still having a physiologic effect. At the other end of the spectrum, if a patient's baseline renin level was 1 or 2 ng/ml/hr, and it is 2 or 3 ng/ml/hr 2 months later, that might be evidence that the renin system in that particular patient is less important in disease pathogenesis for that patient.

I have often wondered what happens when an ACE inhibitor is suddenly withdrawn and the high levels of angiotensin I remain. What probably happens is that the combination of delay and buildup of ACE levels and the spontaneous decay of angiotensin I with circulating peptidases has no major effect. It can be hypothesized that soon after abruptly stopping an ACE inhibitor, there may be a front-loading of angiotensin II, at least briefly. Once all the other factors, such as gradual decay of the drug level and breakdown of angiotensin I, are factored in, I suspect that the effect is probably not physiologically significant.

Participant: Dr. Cody, you are arguing for low doses of ACE inhibitors based on their pharmacokinetics. I know of no studies that compare various doses in terms of clinical efficacy.

Dr. Cody: It has always been difficult to draw firm conclusions regarding dose-response relationships with ACE inhibitors. That is why only a relatively small proportion of physicians use these drugs. Having observed how physicians at many institutions use ACE inhibitors, there is uncertainty about the choice of initial dose strength. A certain dose is given, blood pressure decreases, and then physicians tend to back off, because the effect is too great. Or a small dose is given and no effect is seen, and it is concluded that the ACE inhibitor is not effective in this patient. There is considerable confusion regarding an appropriate initial dose and the criteria for increasing or decreasing the dose.

Dr. Cohn: With all of our expertise, we cannot advise physicians what to do. At the moment, it is impossible to determine the appropriate dose. In the original captopril study, which is probably still the most dramatic demonstration of efficacy in any clinical trial in heart failure, the dose was 300 mg of captopril per day. I always advise physicians to empirically increase the dose if the patient is not doing well, because I am not sure that the results of the original study can be replicated with a low

Participant: More material is probably available in the data bases of the pharmaceutical industry than in the literature with respect to the pharmacokinetics and pharmacodynamics of ACE inhibitors. It is a complicated situation because these drugs bind to a widely distributed enzyme and, in some cases, also bind to other circulating plasma proteins. Therefore, it may be difficult to correlate plasma levels with activity. The general data suggest that at low doses, a substantial degree of ACE inhibition may occur. The manner in which the latter translates to hemodynamic effect and clinical benefit is still unresolved.

Dr. Hirsch: There are scant published data available that discuss the hemodynamic effects of altering plasma

ACE activity. We have recently closely investigated the relationship between the magnitude of plasma ACE inhibition and the associated hemodynamic responses to various ACE inhibitors and have found different threshold effects. A very flat hemodynamic dose response is often apparent; a small dose will decrease blood pressure, but increasing the dose further may not make it any lower since other hormonal systems maintain homeostasis. Overall, plasma ACE activity and the hemodynamic effect can clearly be dissociated during long-term treatment. Thus, if suppression of tissue ACE activity mediates important end-organ effects, the blood pressure dose-response may be an unreliable surrogate end point.

Renal Effects of Angiotensin-Converting Enzyme Inhibition in Congestive Heart Failure

Stephen S. Gottlieb, MD, and Matthew R. Weir, MD

Some studies report that inhibition of angiotensinconverting enzyme (ACE) improves renal function in patients with congestive heart failure, whereas others report that renal deterioration is a frequent complication of treatment with ACE inhibitors. This article explores the mechanisms by which antagonism of the renin-angiotensin system improves kidney function in some patients while causing harm in others. ACE inhibition may after renal blood flow. glomerular perfusion pressure, basement membrane activity and renal tubular function both directly and indirectly. In most patients, renal function is maintained as other neurohormonal mechanisms compensate for the negative effects and permit the positive effects (such as improved renal flow) to predominate. However, when physiologic characteristics or latrogenic interventions (such as volume reduction or prostaglandin inhibition) limit the effectiveness of neurohormonal compensation to maintain renal autoregulation, clinically important deterioration in renal function may occur. An understanding of the renal effects of ACE inhibitors permits their safe and effective use in most patients with congestive heart failure.

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ome investigators¹⁻³ report that inhibition of angiotensin-converting enzyme (ACE) improves renal function in patients with congestive heart failure, whereas others⁴⁻⁶ report that renal deterioration is a frequent complication of treatment with ACE inhibitors. Results of studies of these agents in animal models of heart failure have demonstrated similar variability.^{7,8} This article explores the mechanisms by which antagonism of the renin-angiotensin system improves kidney function in some patients while causing harm in others.

GENERAL EFFECTS OF NEUROHORMONAL ACTIVATION

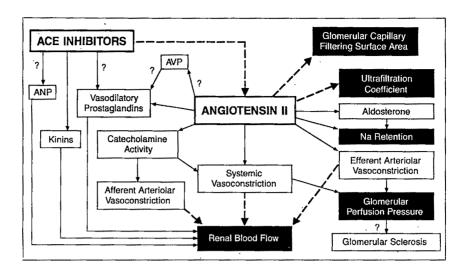
Classically, the renin-angiotensin-aldosterone axis is an endocrine system, the elements of which are secreted by different organ systems. Renin is secreted by the kidney in response to a variety of stimuli (usually hypoperfusion), the renin substrate angiotensingen is produced by the liver and ACE is derived primarily from the capillary endothelium. Renin stimulates the conversion of the propeptide angiotensinogen to angiotensin I, which is subsequently conversed to the most active moiety, angiotensin II, by ACE. Once formed within the circulation, angiotensin II activates its target structures: vascular beds, kidneys, heart, adrenal cortex and noradrenergic nerve endings. The primary purpose of the biochemical cascade is to respond to states of poor perfusion and counteract hypotension by stimulating peripheral vasoconstriction, norepinephrine release, aldosterone formation and sodium reabsorption in the kidney. Moreover, recent biochemical evidence9 suggests that there may be local renin-angiotensin-aldosterone systems within numerous tissues, such as the heart, kidney, adrenal gland, systemic vasculature and brain, which may be involved in the local control of vascular perfusion.

The endogenous neurohormonal systems attempt to compensate for the inability of the failing heart to meet tissue perfusion requirements. In addition to the reninangiotensin-aldosterone axis, catecholamines, arginine vasopressin, prostaglandins and atrial natriuretic peptide are all stimulated in severe heart failure. 10 This neurohormonal activation can have beneficial consequences. For example, the maintenance of arterial blood pressure, vascular volume, inotropic stimulation and improved blood flow at selected organs may be desirable. However, vasoconstriction and fluid retention may result in increased ventricular filing pressures, decreased cardiac output and frequent ventricular arrhythmia. Pharmacologic inhibition of neurohormonal activation provides a physiologic approach to the prevention of harmful consequences. With respect to the renin-angiotensin-aldoste-

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FIGURE 1. The interrelation of the renin-angiotensin system and other neurohormonal systems as it relates to renal function. Continuous arrows indicate stimulation or increases, and dashed arrows indicate inhibition or decreases. Black boxes highlight the net effect on the kidney. ACE = angiotensin-converting enzyme; ANP = atrial natriuretic peptide; AVP = arginine vasopressin.



rone axis, ACE inhibition has been shown to increase survival, ¹¹ improve symptoms, ¹² and decrease arrhythmia ¹³ in patients with congestive heart failure.

RENAL EFFECTS OF NEUROHORMONAL ACTIVATION

The interaction of the multiple neurohormonal systems in the kidney is complex; elevated neurohormonal levels cause both beneficial and detrimental effects. The vasoconstrictor effects of catecholamines decrease renal perfusion by both endocrine and neural actions. 14,15 Arginine vasopressin is also a vasoconstrictor and leads to fluid retention, but systemic increases in arginine vasopressin levels may actually improve renal plasma flow, perhaps by a local effect (at the renal vasculature) on prostaglandins. 16 Prostaglandins, which are produced in response to hypoperfusion and other stimuli, exert important vasodilatory effects that help to maintain renal perfusion: inhibition of prostaglandin production decreases renal blood flow in patients with decreased effective arterial blood volume. 17 In contrast, elevated levels of atrial natriuretic peptide appear to have little functional significance, probably because of receptor down-regulation; they merely reflect the severity of disease. 18 Of all the neurohormonal systems, however, the renin-angiotensinaldosterone system appears to play the pivotal role in determining the renal response to hypoperfusion; it has wide-ranging actions on many kidney components both directly and by interaction with other neurohormonal mediators (Figure 1).

Inhibition of the renin-angiotensin-aldosterone axis may increase or decrease glomerular filtration. When renal perfusion is not dependent on neurohormonal activation, ACE inhibition may lead to enhanced kidney function. However, when physiologic characteristics or iatrogenic interventions (such as volume reduction or prostaglandin inhibition) limit the effectiveness of neurohormonal compensation to maintain renal autoregulation, clinically important deterioration in renal function may occur with ACE inhibition. An improved understanding of the interrelation of the renin-angiotensin-al-

dosterone axis and the renal and neurohormonal compensatory systems in patients with heart failure should minimize the risk of functional renal insufficiency associated with ACE inhibition.

EFFECTS OF ANGIOTENSIN-CONVERTING ENZYME INHIBITION ON RENAL PERFUSION

Renal blood flow is the chief determinant of kidney function in patients with severe congestive heart failure (Figure 2),¹⁹ and the renin-angiotensin system is an important determinant of renal blood flow. The principal contributor to renal vascular resistance is probably the direct vasoconstriction of the large renal arteries by angiotensin II.²⁰ Exogenous angiotensin markedly decreases renal flow when administered systemically, but not when given intrarenally.²¹ Nevertheless, other renal actions of angiotensin II contribute to increased renal

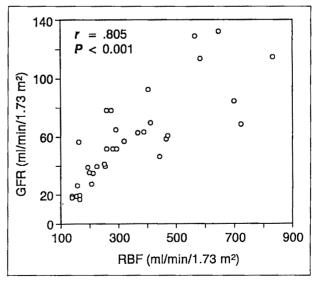


FIGURE 2. The relationship between renal blood flow (RBF) and glomerular filtration rate (GFR) in patients with congestive heart failure not treated with angiotensin-converting enzyme inhibitors. (Adapted from Cody et al.¹⁹)

vascular resistance in patients with heart failure. Angiotensin II may cause both afferent and efferent arteriolar vasoconstriction (with the preponderant effect on the efferent arteriole), and may thereby increase renal vascular resistance and decrease renal blood flow.²² Indirect actions of angiotensin II include potentiation of the vasoconstrictor effects of catecholamines, stimulation of aldosterone production and enhanced thirst. The sympathetic nervous system, like the renin-angiotensin-aldosterone axis, is stimulated in patients with heart failure, and angiotensin II can amplify consequent vasoconstrictive responses. The interrelation of angiotensin II and the sympathetic nervous system is even more complex: neural stimulation may be mediated by local release of angiotersin II.²³ Increased intake of fluid as a result of the dipscgenic effect of argiotensin II, coupled with the salt-retaining effects of aldosterone, may increase the effective arterial blood volume for the kidney by maintaining voume and blood pressure.

Angiotensin II also has a countervailing vasodilatory effect that limits its vasoconstrictive effects in the kidney by direct stimulation of the vasodilatory prostaglandins.^{24,25} However, the net effects of ACE inhibition on renal prostaglancin production are not obvious. The decreased renal perfusion expected from inhibition of the angiotensin II-stimulated prostaglandin release may be mitigated by the direct prostaglandin stimulation that occurs with some ACE inhibitors, notably captopril. 26.27 In one study of patients with heart failure, 28 the administration of captopril increased, not decreased, plasma prostaglandin E2 metabolite levels. In addition, ACE inhibitors are thought to decrease vascular resistance through a reduction in the breakdown of vasodilatory kinins, since the degradative pathway of bradykinin uses the same ACE that is required for the formation of ang-o-

Because systemic increases in arginine vasopressin levels may improve renal plasma flow, and angiotensin II may directly stimulate the production of this neurohormone, ³⁰ ACE inhibitors could theoretically reduce blcod flow to the kidneys in patients with elevated plasma arginine vasopressin levels. However, the effects of angiotensin II on the secretion of arginine vasopressin are disputed; 1 study found no effect. ³¹ The decrease in argin ne vasopressin often seen with ACE inhibition may be an indirect effect of the improvement in the severity of heart failure. ³²

Despite the complex regulation of renal blood flow, it is clear that the net result of ACE inhibition is to limit renal vasoconstriction and improve renal perfusion. First, the direct effects of angiotensin II on the renal arteries and arterioles are blocked. Second, the amplification of the vasoconstrictor effects of catecholamines is blocked. Third, administration of ACE inhibitors results, either directly or indirectly, in less catecholamine activation and lower systemic norepinephrine levels. Fourth, these drugs may prevent neural-induced angiotensin release and arteriolar vasoconstriction. Fifth, ACE inhibitors increase the formation of vasodilatory prostaglandins and decrease the degradation of vasodilatory kinins. Indeed, most studies of the renal effects of ACE inhibitors in

heart failure show improvement or preservation of renal blood flow.¹⁻⁴ To the extent that the glomerular filtration rate is determined by renal blood flow in patients with heart failure, it will improve with ACE inhibition.

EFFECTS OF ANGIOTENSIN-CONVERTING ENZYME ON GLOMERULAR HEMODYNAMICS

The decreased blood pressure often seen after administration of ACE inhibitors to patients with heart failure rarely lowers renal blood flow, but it may have a significant effect on glomerular hemodynamics. Glomerular perfusion pressure is tightly controlled by several autoregulatory mechanisms in order to maintain optimal renal function. However, autoregulation becomes increasingly difficult as mean arterial pressure progressively decreases below 80 mm Hg. and may result in decreased glomerular filtration, renal blood flow and sodium excretion.³³ Nevertheless, glomerular filtration is not totally dependent on renal artery (systemic) pressure in patients with congestive heart failure. No correlation between blood pressure and renal blood flow³⁴ or glomerular filtration rate¹⁹ has been observed in these patients, and vasodilators (such as hydralazine and nitroprusside) may decrease the pressure to very low levels without decreasing glomerular filtration rate or renal blood flow.³⁵

Animal studies suggest that renal dysfunction is found only when hypotension is combined with the efferent arteriolar vasodilation of ACE inhibition. At low mean arterial pressures, angiotensin II is a major autoregulatory hormone essential for maintaining glomerular perfusion pressure. The kidney is able to autoregulate glomerular filtration above a mean arterial pressure of approximately 80 mm Hg without the aid of the reninangiotensin system, but at lower blood pressures plasma renin activity increases.³⁶ In these experimental models, the vasoconstrictor action of angiotensin II at the efferent arteriole was responsible for the observed maintenance or increase in glomerular perfusion pressure and preservation of renal function.³⁷ Thus, under experimental circumstances of poor renal perfusion, renal autoregulation depends on an activated renin-angiotensin-aldosterone system, and the administration of an ACE inhibitor will decrease glomerular filtration even as renal plasma flow increases. 33,38

Unlike experimental studies, clinical investigations evaluating the effects of ACE inhibition on renal function do not consistently support the hypothesis that hypotension must be combined with efferent vasodilation in order for kidney function to deteriorate. In some studies,^{39,40} patients who experienced renal deterioration with ACE inhibitors were hypotensive, but others⁴¹ have demonstrated decreased creatinine and para-aminohippuric acid (PAH) clearance in patients with mean blood pressures above 80 mm Hg. Conversely, improvement in renal function has been noted with a decrease in mean arterial pressure to as low as 67 mm Hg.¹ Nevertheless, the glomerular hemodynamic effects of ACE inhibition exert important adverse effects on the kidney. Both systemic hypotension and efferent vasodilation decrease glomerular perfusion pressure and may limit renal function.

EFFECTS OF ANGIOTENSIN-CONVERTING ENZYME INHIBITION ON THE GLOMERULAR BASEMENT MEMBRANE

Recent studies indicate that, in addition to affecting both renal blood flow and glomerular perfusion pressure. angiotensin II can alter the intrinsic properties of the glomerular membrane. Angiotensin II decreases both the glomerular capillary filtering surface area (by stimulating mesangial cell contractility)⁴² and the ultrafiltration coefficient. Antagonism of the renin-angiotensin-aldosterone system not only prevents these effects of high circulating levels of angiotensin II on the glomerular membrane, but also prevents the decreased ultrafiltration coefficient induced by parathyroid hormone, dibutyryl cyclic-adenosine monophosphate, and other neuroendocrine factors.⁴³ The antiproteinuric effect of ACE inhibition is related to a change in glomerular permselectivity to proteins, a change that may be caused either by glomerular hemodynamic alterations or intrinsic changes of the glomerular basement membrane. Thus, permselectivity is often improved by lowering the glomerular perfusion pressure,44 but ACE inhibition can also improve permselectivity without changing blood pressure, the glomerular filtration rate or renal vascular resistance. 45

The decrease in glomerular perfusion pressure with ACE inhibitors is usually considered an adverse consequence of their use, but it may be beneficial in certain circumstances. Since increased perfusion pressure may cause glomerular sclerosis and progressive renal failure, the chronic decrease in glomerular pressure caused by proximal (renal artery) and distal (efferent arteriole) vasodilation may slow the progression of renal dysfunction in hypertensive and diabetic patients. ^{46,47} ACE inhibition may therefore exert an important beneficial effect at the glomerular basement membrane by 2 mechanisms, improving the glomerular ultrafiltration coefficient and preventing progressive glomerular sclerosis.

EFFECTS OF ANGIOTENSIN-CONVERTING ENZYME INHIBITION ON RENAL TUBULAR FUNCTION

In addition to the stimulation of aldosterone production and consequent sodium retention, angiotensin II may exert a direct effect on renal tubular function. This concept was originally proposed because elevated distal tubule intracellular sodium concentrations were noted after infusions of angiotensin II.⁴⁸ This observation may be the result of a direct tubular effect of angiotensin II or it may be related to an alteration in intrarenal hemodynamics caused by angiotensin II. Supporting the latter concept is the finding that angiotensin II induces greater vasoconstriction in the renal papilla than in the cortex, actions that might preserve medullary hypertonicity and lead to a diminished natriuretic response.⁴⁹

Support for a direct tubular effect comes from studies showing that angiotensin II stimulates sodium transport in isolated rabbit proximal tubules,⁵⁰ and that inhibition of the renin-angiotensin system depresses tubular transport.⁵¹ In addition, angiotensin II binding sites are found in the tubules.⁵² If these tubular effects are important, ACE inhibition may lead to increased diuresis and natri-

uresis by direct impairment of tubular sodium reabsorption.⁵³ Similarly, it was recently reported that captopril improves the hemodynamic and renal response to atrial natriuretic peptide.⁵⁴ Whether this is a direct effect or related to the improved cardiac function after ACE inhibition remains conjectural. Nevertheless, the natriuretic and diuretic effects noted with combined use of ACE inhibitors and furosemide⁵⁵ can assist in controlling the deranged sodium and water metabolism often seen in patients with congestive heart failure.

DETERMINANTS OF THE NET EFFECT OF ANGIOTENSIN-CONVERTING ENZYME INHIBITION ON RENAL FUNCTION

The kidney is able to preserve its function in the face of poor perfusion because of the numerous compensatory neuroendocrine, paracrine and autocrine systems that regulate glomerular filtration. Prostaglandins, the reninangiotensin system, atrial natriuretic peptide, arginine vasopressin and catecholamines all have a part in maintaining renal function. As previously discussed, ACE inhibitors interact with these systems in diverse ways, with both beneficial and deleterious effects on renal function. When compensatory neurohormonal mechanisms cannot maintain effective arterial blood volume to the kidney without angiotensin II, the administration of ACE inhibitor causes functional renal insufficiency. For example, 25 mg of captopril decreases glomerular filtration acutely, but after long-term treatment and time for these compensatory systems to improve circulatory hemodynamics, no change in renal function is noted with the same dose.⁵⁶ Maximal neurohormonal activation before treatment with ACE inhibitors (with consequent inability to provide further compensation) is probably the predominant cause of renal dysfunction with these agents in patients with heart failure who exhibit decreased renal function.

Identification of patients with renal function dependent on activation of multiple neurohormonal systems should indicate those with the greatest risk of functional renal insufficiency with ACE inhibition. Intravascular salt depletion may be the best marker of these high-risk patients. With salt depletion, kinins,⁵⁷ prostaglandins,¹⁶ catecholamines,58 arginine vasopressin16 and the reninangiotensin-aldosterone axis⁵⁹ are all stimulated. If the salt (and consequently volume) depletion is great enough, renal function becomes dependent on all of these systems and further compensatory activity is unlikely. Thus, autoregulation does not occur at low blood pressures in saltdeprived animals given ACE inhibitors, whereas at the same arterial pressures in sodium-replete animals (which presumably do not experience the same extensive neurohormonal activation), autoregulation remains effective. 60 A similar pattern is observed when an inhibitor of vasodilatory prostaglandins is administered to a salt- or volumedepleted human. Aspirin decreases inulin and PAH clearance in salt-depleted persons, but not in sodiumreplete persons who do not require the multiple compensatory neurohormones for preservation of renal perfusion. 17,61

Most clinical studies of patients with heart failure reveal the same pattern; the patients who experience re-

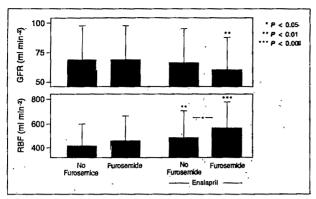


FIGURE 3. The effects on renal blood flow (RBF) and glomerular filtration rate (GFR) of a single dose of furosemide, before and during long-term angiotensin-converting enzyme (ACE) inhibition with enalapril. GFR decreased only when furosemice was combined with ACE inhibition. (Adapted from Cleland et al.⁴⁰)

nal deterioration show evidence of greater neurohormonal activation, often because of salt depletion. Thus, dispensing constant doses of diuretics regardless of clinical condition predisposes a patient to renal deterioration with ACE inhibition. Fimilarly, enalapril decreased the glomerular filtration rate in one study only when furosemide was given immediately before enalapril administration, which also increased plasma renin activity and norepinephrine, arginine vasopressin, aldosterone and angiotensin II levels; enalapril did not adversely affect renal function when given without furosemide (Figure 3). Other studies 1-3.62 have demonstrated that when diuretics are withheld or adjusted carefully, renal function is maintained.

Minimal neurohormonal reserve for the maintenance of renal perfusion may also explain the reports of specific predictors of renal deterioration in patients with heart failure given ACE inhibitors. For example, the high risk of renal dysfunction with ACE inhibitors in patients with hyponatremia⁶³ may be explained by their already maximally stimulated compensatory mechanisms and their inability to activate neurohormones further to maintain renal perfusion. Hyponatremia may be caused by elevated levels of arginine vasopressin, 64 but these patients also have intensely stimulated renin-angiotensin-aldosterone, catecholamine and prostaglandin systems.65,66 In contrast, the deterioration in renal function noted in diabetic patients with heart failure given ACE inhibitors can be attributed to impaired neurohormonal capabilities.⁶⁷ Decreased renin, aldosterone and norepinephrine responses to stress have been noted in diabetic patients.⁶⁸ If a patient is unable to increase renal perfusion by activating compensatory mechanisms, the risk of renal dysfunction with ACE inhibition increases.

CLINICAL RELEVANCE

There are many mechanisms by which ACE inhibitors cause renal dysfunction, but clinical studies^{6,69,70} demonstrate that increasing sodium intake and decreasing diuretic doses reverse most renal problems caused by

these agents. This approach is consistent with the increased risk of functional renal deterioration noted in salt-depleted animals given ACE inhibitors; these drugs worsen renal function in sodium-deplete but not sodium-replete dogs. The Before discounting the use of ACE inhibitors in a patient who develops azotemia with ACE inhibition, the patient's intravascular fluid status should be carefully adjusted so as to maximize effective arterial blood volume to the kidneys. Similarly, short-term administration of ACE inhibitors at the time of massive and quick diuresis may be dangerous and should be avoided. After the patient with heart failure becomes euvolemic, however, the long-term administration of these agents should result in clinical improvement.

The initial response of many physicians to renal dysfunction induced by an ACE inhibitor is to decrease the dose of the drug, a step that has less support in the literature than adjusting the sedium and volume status. While both lowering the dose and decreasing the duration of action of ACE inhibition have been reported to reverse renal impairment caused by these drugs, 39,70 the relation between efficacy and both dose and duration of action has not been well defined. Different organs show different response curves to ACE inhibitors, 72 but whether renal dysfunction can be minimized without decreasing the clinical response to these agents is unknown. Therefore, decreasing the dose of ACE inhibitors should probably be reserved for patients whose renal dysfunction cannot be reversed by adjustment of the sodium and volume status.

Renal dysfunction before administration of ACE inhibitors does not increase the likelihood that renal deterioration will occur. Creatinine clearance in patients who will experience worsening kidney function with ACE inhibitors is not lower than in patients who demonstrate no change or improved renal function.⁶ Similarly, studies that show improvement in renal function with ACE inhibitors have not found that a poor baseline renal function is prognostic of a poor outcome; in fact, one study⁷³ found greater improvement in renal function in patients with a lower initial mean inulin clearance. Although it is reasonable to monitor the degree of azotemia of patients with poor baseline renal function (any deterioration may quickly result in significant impairment), ACE inhibitors should not be withheld from patients simply because of an elevated serum creatinine level. However, an elevated ratio of blood area nitrogen to serum creatinine might reflect intravascular salt depletion and signal the need for careful salt and volume adjustment.

Extreme caution is indicated with the use of nonsteroidal anti-inflammatory agents in patients with heart failure. These agents, which are frequently prescribed in such patients because of concomitant gout, other arthritic disease and general illnesses, may prevent the vasodilatory actions of prostaglandins. This not only may result in deterioration of the heart failure, with a decreased cardiac index and increased pulmonary-capillary wedge pressure, 66 but also may cause renal impairment in patients who depend on the renal vasodilatory effects of prostaglandins. 74 When nonsteroidal anti-inflammatory agents are used in combination with ACE inhibitors, the impair

ment of prostaglandin's renal vasodilatory effects could be particularly dangerous.

CONCLUSION

The kidney is remarkably capable of preserving its perfusion and function in the face of diverse insults. The interaction of multiple neurohormonal systems (involving the action of angiotensin, aldosterone, catecholamines, prostaglandins, kinins, arginine vasopressin and atrial natriuretic peptide) preserves homeostasis under all but the most severe challenges; even with advanced congestive heart failure, end-stage renal disease is rare. The renal dysfunction observed in patients with heart failure after ACE inhibition is typically secondary to iatrogenic interference with the many physiologic mechanisms designed to preserve renal function. By adjusting treatment with consideration as to the volume and neurohormonal status of the patient, deterioration in renal function can be avoided and optimal treatment for congestive heart failure administered.

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DISCUSSION

Dr. Gary Francis (Minneapolis, Minnesota): With regard to the systemic circulation in heart failure, the primary goal of the bcdy is to maintain the blood pressure, even at the expense of diminished cardiac performance. As patients become more ill with congestive heart failure (CHF), it seems that angiotensin II acts primarily to maintain the hydraulic pressure within the glomerulus, which maintains filtration. What happens to patients who are marginally perfused is that they depend on angiotensin II to maintain that hydraulic pressure via efferent constriction. When angiotensin II is blocked, the patients can no longer filter adequately, and they develop temporary renal dysfunction, which seems to be reversible once volume is repleted. I do not think that is inconsistent with what you reported, Dr. Gottlieb, but it is not the same as saying that the patients are unable to mount other neurohormonal responses.

Dr. Stephen Gottileb (Baltimore, Maryland): I agree that these patients are often dependent on angiotensin II for their renal function. The question is, why? Does angiotensin II determine renal function, or are these patients dependent on many neurohormonal systems, and inhibition of any of them may be detrimental? Either of these hypotheses may be correct, but I came to the conclusion that patients with CHF are dependent on multiple neurohormones because of their response to nonsteroidal anti-inflammatory drugs; renal shutdown is not uncommon when these agents are given to patients with CHF. You may be able to inhibit 1 system, but rarely can you inhibit all neurohermonal systems in patients with severe

Dr. Jay Cohn (Minneapolis, Minnesota): Do you think that the system is activated to maintain the kidney, or is the kidney just an innocent bystander in the maintenance of blood pressure. In the study of CHF that we reported in 1981 (Brit Heart J 1981;46:522-527), the systemic blood pressure response to captopril was the primary determinant of renal function. That supports your statements: that the hydraulic pressure perfusing the kidney is the major issue, independent of what is happening intrarenally to the mesangium and the efferent arteriole.

Dr. Gottlieb: I think that the multiple actions of angiotensin II generally protect renal function. Blood pressure alone does not determine renal function. Although renal dysfunction ofter occurs with low blood pressure, there are many exceptions to this in the literature and in clinical practice. It is not just the perfusion pressure or blood pressure that determines renal function.

- Dr. Robert Cody (Columbus, Ohio): Dr. Gottlieb, where does the atrial natriuretic factor (ANF) fit in your scheme?
- Dr. Gottlieb: Although we showed that high levels of ANF were associated with mortality, I believe that ANF is physiologically insignificant in heart failure. The longterm elevations of plasma levels probably lead to tolerance and decreased renal effects.

Hyponatremia and Angiotension-Converting **Enzyme Inhibition**

Dr. Karl Swedberg (Gothenburg, Sweden): It has

been reported that in diabetic patients with low serum sodium levels the combination of diuretics and a long-acting angiotensin-converting enzyme (ACE) inhibitor, such as enalapril, always leads to renal dysfunction. However, in the analysis of the CONSENSUS trial, there was no difference in the incidence of renal dysfunction between the diabetic patients with low serum sodium levels treated with enalapril and diuretics and the placebo group.

When we looked into what happened between baseline and week 2 of treatment, we found that serum creatinine levels increased and then remained stable. The increase was not dependent on baseline creatinine. It occurred in patients with low and with high creatinine levels; it was not possible to tell from the baseline creatinine in which patients it would increase. A 10, 15, or 20% increase in creatinine should be accepted, because it shows that you have actually blocked the system.

- **Dr. Cohn:** Should we be concerned about an increase in serum creatinine? Is a serum creatinine level of 2.5 mg/dl a problem?
- **Dr. Gottlieb:** We do not worry about an increase in creatinine. If the patient is continuing to urinate, is not retaining fluid, and has no clinical renal failure, treatment can be continued. If a problem develops, it should be reversible with adjustment of medications. I would say, however, that we are probably much more tolerant of renal dysfunction than what has been generally accepted in the community.
- **Dr. Cohn:** Let us return to the hyponatremia question. On the one hand, we are constantly warning physicians that a hyponatremic patient is probably hyperreninemic, which will have a profound effect on the initiation of treatment with an ACE inhibitor. Dr. Gottlieb suggested that hyponatremia is a marker for a patient who is going to have trouble with an ACE inhibitor. On the other hand, the hyponatremic patient is a high-renin patient whom you would expect to benefit from an ACE inhibitor. Should we be aggressively treating hyponatremic patients with ACE inhibitors?
- **Dr. Gottlieb:** Both of your points are true. These patients are at high risk, but they also have the most to gain. Fortunately, problems that develop with an ACE inhibitor are almost always reversible with discontinuation of the drug. Starting high-risk patients on low doses of ACE inhibitors should minimize the risk of these agents. The dose can be gradually increased with careful attention to the patient's fluid status. If we can treat these high-risk

patients with ACE inhibitors, which is usually possible, the benefit may be enormous.

- **Dr. Cohn:** You believe that they should definitely be treated with an ACE inhibitor.
- **Dr. Gottlieb:** The adverse renal effects of ACE inhibition are generally related to hemodynamic factors. I think that most of the concern about hemodynamic deterioration is a result of the common practice of starting ACE inhibitors at the same time as massive diuresis. These patients often have significant adverse experiences. ACE inhibitors are long-term agents and should be started after the patient is euvolemic.
- Dr. Cody: It is not sufficient to consider what an ACE inhibitor is doing of itself; it is important to consider the effects of an ACE inhibitor under varying salt conditions. If you are treating a patient with a large dose of a diuretic, his or her baseline blood urea nitrogen (BUN) or creatinine levels will be higher. With addition of an ACE inhibitor, the BUN and creatinine levels can be lowered in most cases by decreasing the diuretic dose, without changing the ACE inhibitor. When the response to an ACE inhibitor was studied under conditions of differing sodium intake, but at the same dose of an ACE inhibitor, one could predict that the glomerular filtration rate and renal blood flow would vary according to whether the patient was receiving diuretics, and probably hyponatremic versus relatively normal sodium intake. This has been demonstrated in sodium balance studies conducted in patients with heart failure treated with ACE inhibitors.
- **Dr. Gottlieb:** I agree. In clinical practice, the best thing to do is adjust the patient's sodium and volume status.
- **Dr. Cohn:** Dr. Gottlieb, from your physiologic description of the ACE inhibitor's activity, one might expect that they would produce a natriuresis and would actually decrease the need for a diuretic. In most studies, however, that has not appeared to be an important effect. There may be a modest reduction in diuretic need in some patients, but it is certainly not a very dramatic effect.
- **Dr. Gottlieb:** There is a wide variation of diuretic effect among patients. The various actions of ACE inhibitors at the renal artery, afferent and efferent arterioles, renal tubule and basement membrane have conflicting consequences, which makes prediction of the net natriuretic effect difficult.
- **Dr. Swedberg:** In the CONSENSUS trial, diuretics were needed less often in the enalapril group than in the placebo group.

Potential Role of the Tissue Renin-Angiotensin System in the Pathophysiclogy of **Congestive Heart Failure**

Alan T. Hirsch, MD. Yigal M. Pinto, Heribert Schunkert, MD, and Victor J. Dzau, MD

The circulating regin-angiotensin system (RAS) plays an important role in the maintenance of cardiovascular homeostasis. It has recently been demonstrated that endogenous RAS exist in target tissues that are important in cardiovascular regulation. This article reviews the multiple effects of angiotensin II in target tissues, the evidence for the presence of functional tissue RAS and the data that suggest a role for these tissue RAS in the pathophysiology of heart failure. Activation of circulating neurohormones is predictive of worsened survival in heart failure: bowever, cardiac and renal tissue RAS activities are also increased in the compensated stage of heart failure, when plasma renin-angiotensin activity is normal. It is hypothesized that the plasma RAS maintains circulatory homeostasis during acute cardiac decompensation, while changes in tissue RAS contribute to homeostatic responses during chronic sustained cardiac impairment. This concept of different functions of circulating and tissue RAS in the pathophysiology of heart failure may have important pharmacologic implications.

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THE RENIN-ANGIOTENSIN SYSTEM IN CARDIOVASCULAR HOMEOSTASIS

The circulating renin-angiotensin system (RAS) is activated during states of sodium restriction, hemorrhage or intravascular volume contraction, during an increased adrenergic state or as a consequence of acute cardiac decompensation. The effects of this endocrine system are mediated by the pestide hormone angiotensin II, which elicits tissue-specific responses at many target organs, including the blood vessels, kidney, heart, brain and adrenal tissues. Angiotensin receptors in target tissues mediate systemic vasoconstriction, adrenal aldosterone releasz, hypophyseal vasopressin secretion and renal sodium reabsorption. The circulating RAS, as a classic hormonal system, is subject to feedback regulation and serves to maintain acute cardiovascular homeostasis.

The important role of the circulating RAS in the maintenance of cardiovascular homeostasis has been defined by use of specific antagonists. Antirenin antibodies, ² angiotensin II antagonists³ and, more recently, inhib tors of angiotensin-converting enzyme (ACE)⁴ have each been used in this context. Studies with these agents have demonstrated that acute hemodynamic responses may be predicted by the pretreatment plasma RAS activity. In contrast, long-term responses to these agents are not predicted by plasma RAS activity. For example, ACE inhibition has been reported to be beneficial in pathophysiologic states characterized by the absence of activation of the circulating RAS. ACE inhibition elicits hypotensive responses in normal-renin essential hypertensicn⁵ or in low-rer in hypertension that occurs after bilateral nephrectomy.6 These agents are also effective in patients with hear-failure and normal plasma RAS activity.^{7,8}

It has recently been demonstrated that endogenous RAS exist in target tissues that are important in cardiovascular regulation. The possibility that these tissue RAS might contribute to local angiotensin II production has important pathophysiologic and therapeutic implications. The altered regulation of these systems (in blood vessels, cardiac and renal tissues) in pathophysiologic states has been the focus of our recent investigations. In this article, we review the multiple effects of angiotensin II in target tissues, the evidence that supports the presence of functional tissue RAS and the increasing body of data that suggests a role for these tissue RAS in the pathophysiology of heart failure.

ANGIOTENSIN II AS A MULTITARGETED BIOLOGIC MEDIATOR

The detailed cellular mechanisms by which angiotensin II alters tissue functions is beyond the scope of this article. However, alteration of tissue function by angiotensin II may be mediated via specific membrane-bound angiotensin II receptors, via angiotensin II's effects on nuclear receptors, via the modulation of adrenergic tone or by interactions with other local mediators. Both the circulating and tissue RAS contribute to altered endorgan responses by the relative summation of these effects.

Direct effects: Angiotensin II exerts its physiologic effects via specific receptors that are widely distributed throughout the vascular tree. Angiotensin II induces vascular contractions in isolated aortic strips, as well as in isolated vascular rings from femoral, carotid and coronary vascular beds. Angiotensin II-receptor binding activates phospholipase C, which increases the hydrolysis of phosphatidylinositol biphosphate to diacyl glycerol and inosityl triphosphate. These second messengers modulate calcium-sensitive protein kinase and cytoplasmic calcium concentrations.

Cardiac angiotensin II may also exert its effects via cell membrane angiotensin II receptors, whose presence has been confirmed in myocyte cell culture¹⁰ and in human myocardial tissue.¹¹ The physiologic effects of angiotensin II on cardiac function have been examined. In vivo, the direct cardiac effects of angiotensin II have been difficult to isolate from systemic effects. In vitro, in isolated cardiac muscle strips from cats, angiotensin II causes a dose-dependent increase in contractility in 10⁻¹⁰ to 10⁻⁵ M concentrations. 12,13 This direct positive inotropic effect is not dependent on adrenergic potentiation, since the responses were not altered by pretreatment with reserpine, adrenergic antagonists or prior sympathetic denervation. 14,15 These effects are elicited in part via potentiation of the slow inward calcium current by angiotensin. 10,15-17 In contrast to effects on the strength of contraction, angiotensin II has little direct effect on the chronotropic response of the heart. Whereas coronary vasodilation would usually accompany the increased myocardial oxygen consumption associated with an increased inotropic state, potent direct constrictor effects of cardiac angiotensin II on coronary vasculature predominate.18

Angiotensin II also exerts important effects on kidney functions, that is, regulation of intrarenal hemodynamics and preservation of salt and water homeostasis. $^{19-21}$ Sodium delivery may be altered because angiotensin II causes potent renal vasoconstriction. 22 Preferential efferent arteriolar vasoconstriction by angiotensin II may increase transglomerular hydrostatic pressure and the filtration fraction. These physiologic responses may preserve glomerular filtration rate in the setting of decreased renal blood flow. Additionally, angiotensin II may elicit decreases in glomerular capillary surface area by contracting glomerular mesangial cells, thereby increasing the ultrafiltration coefficient, $K_{\rm f}$. 23,24 Angiotensin II may di-

rectly stimulate proximal tubular sodium reabsorption by activating the sodium/hydrogen antiporter. ^{25,26} Finally, nanomolar angiotensin II concentrations increase sodium and bicarbonate reabsorption via alterations in phospholipase C-induced calcium transients. ^{27,28}

In addition to its direct effects on tissue function, angiotensin II may promote end-organ remodeling. Angiotensin II has been reported to have growth-promoting effects in cultured 3T3 fibroblasts, vascular myocytes and cardiac myocytes. Angiotensin II may stimulate the proliferation of cultured human vascular smooth muscle cells when grown in serum;²⁹ however, only protein synthesis without cell division has been demonstrated when rat aortic smooth muscle cells were studied in serum-free medium.³⁰ Naftilan et al³¹ have reported that angiotensin II can directly induce the expressions of the proto-oncogenes c-fos, c-myc and c-jun, as well as the mitogen platelet-derived growth factor. A recent report³² demonstrates that angiotensin II similarly induces proto-oncogene expression and hypertrophy of cultured cardiac myocytes. These effects of angiotensin II on growth in vivo are supported by data demonstrating that long-term ACE inhibition can reverse both cardiac and vascular hypertrophy.³³⁻³⁵

Indirect tissue effects via other neuroendocrine systems: Local angiotensin II may also contribute to tissue function via effects transduced by other neuroendocrine systems. Angiotensin II has been shown to amplify catecholamine release from noradrenergic nerve endings, thereby augmenting vascular tissue responses to sympathetic activation.³⁶⁻³⁹ Gimbrone and Alexander⁴⁰ have demonstrated that prostacyclin synthesis by cultured cells is increased by angiotensin II. Endothelium-dependent vasorelaxant effects of angiotensin, mediated by local prostacyclin production, have been demonstrated in canine renal arteries. 41 Angiotensin II may also increase the release of endothelium-dependent relaxant factor. 42 Conversely, catecholamines and prostaglandins modulate local angiotensin II production. For example, β_2 -adrenoreceptor activation increases angiotensin II release from the isolated mesenteric vascular bed.³⁹

Angiotensin II also exerts indirect effects on the kidney that may amplify or modulate its receptor-mediated effects. For example, angiotensin has been shown to alter the biosynthesis or release of vasopressin, atrial natriuretic factor and aldosterone. 43-45 Angiotensin II has also been demonstrated to be important for mediating the vasoconstrictor and antinatriuretic effects of renal nerve stimulation. Inhibition of angiotensin II synthesis by ACE inhibition blocks adrenergic-mediated increases in afferent and efferent vascular resistance, and preserves single nephron and whole kidney plasma flow and filtration rate. 46,47 The glomerular and renovascular responses to angiotensin II are also markedly decreased by renal denervation.⁴⁸ Thus, the full physiologic expression of angiotensin II's renal effects is dependent on intact renal sympathetic function. In addition to angiotensin's indirect renal vasoconstrictor effects, this peptide also modulates vasodilator hormones. Renal prostaglandins are in-

A SYMPOSIUM: ACE INHIBITION IN CONGESTIVE HEART FAILURE

creased during long-term administration of angiotensin II, ⁴⁹ and might contribute to the maintenance of glomerular filtration by decreasing afferent arteriolar resistance. ⁵⁰ This is a accord with the concept that there is a dynamic interplay in the effects of vasoconstrictor and vasodilator hormones, and that this relationship may be important in the local regulation of renal function.

Angiotensin II may also promote vascular and cardiac myocyte growth indirectly via its adrenergic effects. Catecholamines stimulate the growth of rat aortic vascular smooth muscle cells⁵¹ and also induce polyploidy of these cells in tissue culture.⁵² Angiotensin II-induced norepinephrine release should be capable of inducing cardiac myocyte growth and stimulating the expression of the proto-oncogene c-myc.⁵³ Thus, via both direct effects and via signals transduced by other local hormonal systems, angiotensin II serves as a multitargeted biologic peptice.

SITES OF ANGIOTENSIN II PRODUCTION

Circulating renin-angiotensin system: According to the concept of an endocrine system, plasma angiotensin II is presumably produced via the angiotensinogen-renin-ACE biochemical cascade in the systemic or pulmonary circulation. The angiotensin II peptide is then delivered via the circulation to distant target organs throughout the body.

Tissue renin-angiotensin system: This emerging concept proposes that angiotensin II is produced in target organs via local RAS biochemical cascades. Renin substrate, renin-like enzymatic activity and ACE have each been demonstrated at tissue sites by immunohistochemical and biochemical techniques. ⁵⁴⁻⁵⁶ Molecular biologic techniques have confirmed that both renin and angiotensinogen genes are expressed in many tissues associated with cardiovascular homeostasis, for example, blood vessels, heart, kidne√, brain and adrenal tissues. ^{57,53} In addition, there is evidence for uptake of renin and angiotensinogen by the vessel wall. ^{59,60} The evidence supporting the existence and physiologic role of vascular, cardiac and renal RAS is reriewed next.

Vascular renin-angiotensin system: The existence of renin, angiotensinogen and angiotensin II in blood vesse s has been reported by a number of laboratories. 61,62 The vessel wall distribution of renin has been demonstrated by use of antirenin-specific antibody; these studies have demonstrated intense staining throughout the thickness of the aorta and large and smaller arteries, as well as arterioles, particularly in endothelial and smooth muscle cells. 63 The function of the vascular RAS has been suggested by many studies. Oliver and Sciacca⁶⁰ demorstrated that the is plated rat hindlimb artery was capable of generating angiotensin II from tetradecapeptide renin substrate in the absence of circulating renin. Local syrthesis of angiotersin II, in isolation from the circulatior, was demonstrated by Mizuno et al.⁶⁴ In this preparatior, long-term oral captopril treatment decreased angiotensia II release from the isolated leg vasculature. Tissue angictensin synthesis is further suggested by the presence of angiotensin II in rat plasma 48 hours after bilateral nephrectomy, when plasma renin activity is undetectable. 65 Additionally, kinetic analysis of the in vivo arterial-venous angiotensin I and angiotensin II differences in sheep and humans also supports the concept of vascular tissue angiotensin II production.^{66,67}

The local synthesis of angiotensin II in the blood vessel wall may have important physiologic implications. As previously noted, local angiotensin II may contribute directly to regional blood flow regulation by activating specific vascular receptors in regional circulations (e.g., the kidney). Alternatively, angiotensin II may alter vascular function via its effects on norepinephrine release from noradrenergic nerve terminals or via local hormonal effects. Thus, the net effect of tissue RAS activity in an individual vascular bed is dependent on the relative contributions of angiotensin's direct and indirect effects. In pathophysiologic states in which the neuroendocrine systems are not activated (e.g., chronic stable heart failure), these local tissue mechanisms may predominate.

Evidence to support the importance of local angiotensin II to arteriolar and conduit artery function is derived from experiments involving blockade of renin or angiotensin effect. Longnecker et al⁶⁸ demonstrated that topical administration of saralasin to the microvasculature of the spontaneously hypertensive rat, which presumably elicits only local effects, resulted in selective vasodilation of third- and fourth-order arterioles; thus, local angiotensin II synthesis may vary depending on the size of the blood vessel and circulatory region studied. The potential roles of vascular tissue RAS are supported by additional studies of hypertensive models. Prolonged infusion of saralasin normalizes blood pressure in the chronic phase of 2-kidney, 1-clip hypertension and the hypotensive response is not correlated with the pretreatment plasma renin activity.69 In the chronic phase of hypertension in this model, plasma renin activity is near normal, but vascular ACE activity is increased. This increased vascular ACE activity is responsible for the increased vasoconstrictor response to angiotensin I infusion.⁷⁰ Further evidence to support the contribution of vascular tissue RAS activity to blood pressure control is provided by the data of Unger et al.⁷¹ In this study, the investigators observed a prolonged hypotensive response after withdrawal of chronically administered ACE inhibitors, despite the earlier return of plasma ACE activity to normal values. These data suggest that inhibition of plasma ACE activity is not essential to elicit a systemic hypotensive response. In fact, in some of these studies, sustained inhibition of vascular ACE activity has been observed in parallel to the blood pressure response. These data suggest that inhibition of arteriolar ACE may underlie the antihypertensive effect. In humans, the compliance and diameter of large (brachial and carotid) arteries is increased by ACE inhibition, even at doses that are without a systemic hypotensive response. 72,73 The latter observation suggests that local vascular RAS activity influences the buffering function of these conduit vessels. This effect of vascular RAS on arterial compliance may result in decreased ventricular afterload when ACE inhibitors are administered. Thus, multiple lines of evidence suggest that local vascular synthesis of angiotensin II exerts physiologically important responses in normal and hypertensive states.

Cardiac renin-angiogensin system: The presence of RAS components in the heart has also been demonstrated by enzymatic, biochemical and molecular biologic techniques. Renin enzymatic activity has been demonstrated in isolated cardiac myocytes.⁵⁴ Cardiac renin and angiotensinogen messenger ribonucleic acid (mRNA) expressions have been identified in the heart. 74,75 The presence of ACE has also been demonstrated in the rat heart. 76-78 Recent data suggest that cardiac ACE is synthesized locally;79 ACE is located throughout cardiac tissues, but is greatest in the atria, vasculature, conduction system and cardiac valves. 80 The demonstration of conversion of angiotensin I to angiotensin II by the isolated rat heart provides evidence that tissue angiotensin II can be locally synthesized.81 In this ex vivo system, ACE inhibitors attenuate the angiotensin conversion.82 Other non-ACE enzyme peptidases may also contribute to the generation of angiotensin II in the heart, since angiotensin I to angiotensin II conversion has been recently reported to occur in failing human hearts and cardiomyopathic hamster cardiac tissues.83,84

The activity of the cardiac RAS can be modulated by various physiologic perturbations. For example, the expressions of both angiotensinogen and renin are increased in the hearts of sodium-depleted animals. We have also observed that cardiac renin expression is selectively increased in response to the infusion of isoproterenol (unpublished data). The dietary sodium restriction, diuretic use and activated sympathetic nervous system that may accompany clinical hypertension and heart failure may therefore increase myocardial RAS activity. As discussed earlier, local angiotensin II may then have important effects on the cardiac inotropic state, ventricular relaxation or myocyte growth.

Renal renin-angiotensin system: The presence of an RAS system in the kidney has also been documented by molecular biologic, immunocytochemical and biochemical techniques. Taugner et al^{86,87} have detected renin in afferent and efferent arterioles and in smaller amounts in the proximal tubule by antirenin antiserum staining. Cultured glomerular mesangial cells synthesize renin.88 Angiotensinogen mRNA expression in the renal cortex has been demonstrated and in situ hybridization studies have shown that angiotensinogen mRNA is expressed principally in the proximal tubule;89,90 renin mRNA is primarily localized in the juxtaglomerular cells. 91,92 Intrarenal ACE has also been demonstrated by the presence of the ACE mRNA.93 In addition to the vasculature, ACE has been localized in the proximal tubule brush border by immunohistochemical and radioligand binding studies. 94,95 Since all the components are found in the proximal tubule, local angiotensin II synthesis has been hypothesized.⁹² Indeed, a recent micropuncture study⁹⁶ demonstrated that the proximal tubular fluid angiotensin II concentration is 1,000-fold greater than that in the plasma. Local angiotensin II production might be a major factor in regulation of basal renal hemodynamics and sodium reabsorption; this local system is also responsive to physiologic stimuli. Tissue-specific regulation has been

demonstrated in response to sodium depletion and glucocorticoid and androgen administration. 90,97,98 This intrarenal RAS may thereby be important in the regulation of sodium homeostasis and glomerular filtration in, for example, heart failure.

POTENTIAL ROLES OF CIRCULATING AND TISSUE RENIN-ANGIOTENSIN SYSTEM IN HEART FAILURE

It is well documented that a reduction in cardiac output elicits compensatory homeostatic responses that are mediated by neurohormonal mechanisms. Activation of the sympathetic nervous system results in systemic vasoconstriction, decreases in renal blood flow and glomerular filtration rate and an increase in tubular reabsorption of sodium.⁹⁹ Activation of the RAS contributes further to the increases in vascular tone and sodium avidity. Vasopression secretion may also be increased during marked reductions in cardiac output, which contributes significantly to the antidiuretic state of heart failure. 100-102 The temporal activation of circulating neurohormonal mechanisms was well illustrated in the study by Watkins et al¹⁰³ of the experimental canine model of cardiac decompensation. In this model, reductions in cardiac output and filling pressure result in elevations of plasma renin activity and angiotensin II and aldosterone levels, with associated vasoconstriction and sodium retention. However, these circulating neurohormonal mechanisms return to normal during the compensated stage of heart failure as plasma volume and cardiac stroke volume increase. Additionally, in other animal models of compensated heart failure, such as the coronary-ligated rat or subacute stage of canine rapid ventricular pacing, normal or near-normal plasma renin activity and angiotensin II levels have been demonstrated. 76,101,104 Thus, in experimental heart failure, circulating neurohormonal mechanisms exhibit a time-dependent response, with acute activation during cardiovascular decompensation and subsequent normalization during the chronic, compensated phase (Figure

A similar pattern of activation of plasma neurohormones has been observed in patients after acute myocardial infarction¹⁰⁵ or during heart failure.^{7,106} Patients with mild heart failure or stable disease usually demonstrate normal plasma renin activity, catecholamines and vasopressin levels at rest. Nevertheless, long-term ACE inhibition elicits salutary responses from both patients and animals with stable cardiac dysfunction. Overall morbidity is decreased and survival may be prolonged. We hypothesize that during the compensated phase, the tissue RAS may contribute to the pathophysiology of heart failure. Examination of the role of the tissue RAS in this disease state may also provide insights into the mechanisms mediating these beneficial therapeutic responses to ACE inhibition.

Vascular renin-angiotensin system in heart failure: Little is known of the activity of the RAS in the blood vessel in heart failure. As discussed, local vascular angiotensin II can cause constriction of large arteries and resistance vessels, resulting in increased systemic vascular re-

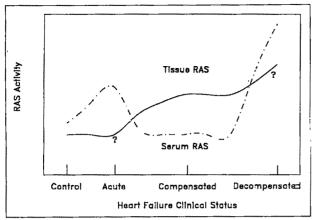


FIGURE 1. The relative contributions of the plasma and tissue renin-angiotensin systems (RAS) during the natural history of heart failure. Acute cardiac decompensation activates the circulating RAS; the acute response of the tissue RAS is not known. During compensated heart failure, tissue RAS are activated and the circulating RAS activity has been shown to be normal. The circulating RAS is again activated during endstage or decompensated states; further activation of the tissue RAS is hypothesized in this condition. (Reprinted, with permission, from Heart Failure and Arrhythmias.¹³¹)

sistance and reduced arterial compliance. These effects may increase ventricular afterload, and thereby increase myocardial wall stress. Local angiotensin II formation in venous capacitance vessels may also contribute to increased preload. Thus blockade of the effect of vascular RAS by ACE inhibition may decrease preload, arterial compliance and vascular resistance. Captopril also elizits preferential renal and splanchnic vasodilation in these animals, as in patients with heart failure. 107 Additionally, ACE inhibition elicits venodilation, increased venous compliance and decreased intravascular volume. 108 These decreases in cardiac preload and afterload, as well as normalization of regional blood flow, may also be beneficial in blunting cardiac dilation after myocardial infarction. The potential effects of the vascular RAS in heart failure are summarized in Table I.

Cardiac renin-angiotensin system in heart failure: While increased vascular RAS activity may contribute to the increase in afterload in heart failure, the contribution of cardiac RAS activity in pathophysiologic states has only recently been investigated. We have recently studied cardiac ACE activity in rats with left ventricular hypertrophy induced by aortic banding, 79,81 and found a marked rise in cardiac ACE activity and ACE mRNA

TABLE I Poter tial Contributions of the Vascular ReninAngiotensin System to the Pathophysiology of Heart Failure

Pathophysiologic
Consequences

Decreased conduit vessel Increased afterload compliance & increased arteriolar resistance
Venoconstriction Increased preload
Renal and splanchnic Regional blood flow vasoconstriction redistribution

expression and an associated increase in the cardiac conversion rate of angiotensin I to angiotensin II.

We have also recently demonstrated⁷⁶ that cardiac ACE is elevated in the chronic compensated state of experimental heart failure in the rat. The ACE activity is increased in the right ventricle and interventricular septum, and correlates with the extent of the infarct and the degree of cardiac dilatation. As in stable human disease, circulating renin and ACE activities are not elevated during the chronic compensated phase in this animal model. The increase in right ventricular and interventricular septal ACE activities in rats with experimental heart failure is probably due to the induction of ACE expression with increased local enzyme synthesis; however, the exact stimulus for the induction of cardiac ACE is unclear. In this model of heart failure, Drexler et al^{109,110} have also demonstrated induction of the expression of angiotensinogen and atrial natriuretic factor in the ventricular myocardium in proportion to the extent of myocardial infarction. It is possible that an increase in ventricular dimension or wall tension may be a direct stimulus, or that increased myocardial neurosympathetic activity is responsible for the induction of cardiac RAS expression.

The increase in cardiac ACE activity in the hypertrophied or failing myocardium may have important pathophysiologic implications. Functional angiotensin II receptors have been demonstrated in the myocytes of normal and failing human hearts. 11 As noted earlier, angiotensin II may elicit intense coronary artery vasoconstriction. Indeed, the coronary vasodilatory effect of ACE inhibitors, independent of circulating angiotensin II, has been demonstrated in the isolated perfused heart by both Linz et al82 and Van Gilst et al.111 Locally synthesized cardiac angiotensin II may also directly influence the cardiac inotropic state^{12,13,15} or indirectly augment cardiac systolic function via facilitation of norepinephrine release from sympathetic nerve terminals. 112,113 In the failing heart, it is expected that these tissue effects may be especially important.

Foult et al114 have extended these observations to human heart failure by examining the effects of intracoronary infusion of enalaprilat on indices of systolic performance. Inhibition of cardiac ACE activity caused a significant decline in the ejection fraction and the cardiac index and decreased the end-systolic stress/end-systolic volume ratio in patients with idiopathic dilated cardiomyopathy. Coronary vascular resistance also decreased, suggesting that basal tissue angiotensin II concentrations subserved inctropic and corcnary vasoconstrictive responses. Since there may be other non-ACE biochemical pathways for angiotensin I to angiotensin II conversion in the heart, cardiac tissue angiotensin II generation might still occur despite administration of systemic ACE inhibitors. Thus, tissue angiotensin I synthesis could potentially provide positive inotropic effects despite systemic ACE inhibition.83,84 Finally, local angiotensin II may also modulate diastolic function. In hypertrophied rat myocardium studied as a Langendorff preparation, infusion of angiotensin I induces a dose-dependent increase in left ventricular end-diastolic pressure.81

Cardiac angiotensin may also participate directly in ventricular hypertrophy and remodeling via its growth-promoting effects. ^{31,32} Angiotensin II has been shown to stimulate cardiac myocyte growth. In addition, the enhanced norepinephrine release may also promote cardiac hypertrophy. These observations may underlie the ability of ACE inhibitors to produce regression of cardiac hypertrophy secondary to chronic hypertension. ^{34,115} Thus, the increased cardiac ACE activity and locally synthesized angiotensin II may also participate in the ventricular remodeling that is ultimately responsible for cardiac dilation after myocardial infarction or in everload conditions.

Enhanced cardiac angiotensin II generation may also contribute to the increased ventricular dysrhythmias that are characteristic of advanced cardiac dysfunction. In the isolated perfused rat heart, Linz et al82 have demonstrated that both angiotensin I and angiotensin II perfusion aggravated the arrhythmias induced by transient ischemia. The dysrhythmias induced by angiotensin I administration were abolished by pretreatment with the ACE inhibitor ramipril. It is not known whether the dysrhythmias associated with impaired left ventricular function are due to either subendocardial ischemia, altered adrenergic state or direct effects of angiotensin on the conduction systems. Indeed, a high density of angiotensin II binding sites has been detected in the conduction system. 116 Clinical trials of ACE inhibition in patients with heart failure are under way and should help to determine whether sudden death, which is presumably a marker of high-grade dysrhythmias, is altered by this modality. The possible roles of the cardiac RAS are listed in Table II.

Renal renin-angiotensin system in heart failure: We have recently observed that experimental heart failure changes the activity of the intrarenal RAS.¹¹⁷ In the chronic state after experimental myocardial infarction in the rat, the renal angiotensinogen mRNA level is increased twofold compared with sham-operated controls.¹¹⁷ The magnitude of increase correlated closely with the histopathologic size of the myocardial infarction, implying a relation with the degree of ventricular dysfunction.

The effect of heart failure on the kidney RAS was selective for this single component of the RAS, since renal renin and ACE activity were unchanged. Interestingly, long-term ACE inhibition with enalapril normalized renal angiotensinogen expression to that of sham-operated control rats, suggesting that angiotensin may have a positive feedback role on angiotensinogen expression in the kidney. The increased renal angiotensinogen expression may result in increased intrarenal angiotensin II levels that may mediate sodium reabsorption and vasoconstriction and increase the filtration fraction. Thus, ACE inhibition would block both systemic and intrarenal angiotensin II formation. These data may explain why treatment with ACE inhibitors elicits renal vasodilation and natriuresis despite normal activity of the circulating RAS. 118,119 The possible roles of the renal RAS are depicted in Table III.

Tissue renin-angiotensin system—a hypothesis: As reviewed earlier, activation of circulating neurohormones

TABLE II Potential Contributions of the Cardiac Renin-Angiotensin System to the Pathophysiology of Heart Failure

Potential Tissue Effect	Pathophysiologic Consequences
Direct cellular angiotensin	Positive inotropic effect
II effects	Diastolic dysfunction
Facilitate adrenergic state	Positive inotropic effect
-	Dysrhythmia induction
Coronary artery vasoconstriction	Subendocardial ischemia
Proto-oncogene expression	Cardiac hypertrophy and remodeling

has been demonstrated to be predictive of worsened survival. 120,121 However, we and others have shown that cardiac and renal tissue RAS activities are also increased in the compensated stage of heart failure at a time when plasma renin-angiotensin activity is normal. Therefore, we hypothesize that the plasma RAS serves to maintain circulatory homeostasis during acute cardiac decompensation, while changes in tissue RAS contribute to homeostatic responses during chronic sustained impairment of cardiac function (Figure 1). The increase in cardiac and renal RAS activities (and tissue angiotensin II formation) during stable heart failure may mediate compensatory local cardiac inotropic effects, redistribution of regional blood flow and renal sodium retentive effects. Activation of angiotensin biosynthesis locally may permit tissue homeostatic responses to occur without detrimental effects of systemic neurohormonal activation. Whether sustained activation of tissue RAS systems during the compensated stage contributes to disease progression in heart failure is not known. We hypothesize that progressive cardiac decompensation would lead to further activation of both tissue RAS and circulating neurohormonal systems (Figure 2). This concept of differential temporal contributions of circulating and tissue RAS to the pathophysiology of heart failure may have important pharmacologic implications.

CIRCULATING AND TISSUE RENIN-ANGIOTENSIN SYSTEM AS TARGETS OF DRUG ACTIONS

Inasmuch as local formation of angiotensin II in tissues may contribute to abnormalities in vascular, cardiac and renal function in heart failure, inhibition of these systems is likely to mediate the benefits of pharmacologic therapy in this disease state (Table I). Thus, in animal models of heart failure and in clinical disease, ACE inhib-

TABLE III Potential Contributions of the Renal Renin-Angiotensin System to the Pathophysiology of Heart Failure

Potential Tissue Effect	Pathophysiologic Consequences
Proximal tubule sodium reabsorption Efferent arterial vasoconstriction	Increased plasma volume RBF ↓ GFR ++ ↑
GER = glomerular filtration rate: RRE = region	

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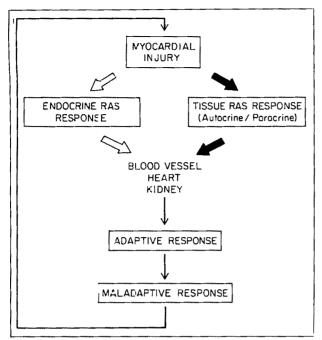


FIGURE 2. Potential pathophysiologic roles of the tissue and circulating renin-ingiotensin systems (RAS) during heart falure. Myocardial injury and cardiac decompensation are postulated to activate both endocrine RAS and autocrine/paracrine tissue RAS responses, though these may not occur synchronously. Increased preload and afterload (vascular RAS), positive inotropic and negative lucitropic effects (cardiac RAS) and increased plasma volume (renal RAS) may serve as homestatic responses. These responses may eventually become maladaptive, leading to further myocardial injury.

itors demonstrate efficacy despite normal plasma renin activity. Whereas the acute vasodilatory response to an ACE inhibitor is influenced by the activity of the circulating RAS, the long-term hypotensive response to ACE inhibitors may be more dependent on inhibition of tissue ACE activity.

Local RAS activity may elicit important end-organ effects; it is attractive to speculate that these systems may explain differential pharmacologic effects of ACE inhibitors. Experimental data demonstrate that plasma pharmacokinetics co not predict the tissue half-life of these agents. For example, captopril administration to spoutaneously hypertensive rats inhibits blood vessel and renal ACE for days longer than its plasma effects. 77 Captopril, fosinopril and zofenipril have been reported to produce greater and more prolonged inhibition of spontaneously hypertensive rat cardiac ACE after a single oral cose than ramipril and enalapril. 122 Similar disparities in tissue ACE inhibition by various agents have been demonstrated in brain and renal tissue. The tissue pharmacokinetics of ACE inhibitors in humans are not known

Thus, target tissue penetration or binding by these agents to ACE may underlie clinically important effects. Neither the pretreatment plasma renin activity nor the acute hypotensive response to ACE inhibition precicts long-term efficacy in heart failure patients.8,123 It has been suggested that long-acting ACE inhibitors (e.g.,

enalapril) may have greater adverse effects on renal function than short-acting agents. 124 These adverse effects were attributed to more prolonged systemic hypotension than occurred with shorter-acting agents. However, true equipotent doses for tissue ACE inhibition are difficult to achieve in these studies. The inability to define tissuespecific ACE-inhibition equipotency in clinical trials may also explain, ir part, the recent reports of disparate effects of captopril and lisinopril on left ventricular ejection fraction in patients with heart failure¹²⁵ and the differing effects of these agents on exercise duration. For example, it has been suggested that the ability of long-term ACE inhibition to improve skeletal muscle blood flow is due to effects on vascular RAS activity. 126

SUMMARY

Tissue RAS may contribute to the pathophysiology of heart failure via myocardial RAS effects, effects on afterload (vascular RAS activity) and effects on preload (vascular and renal tissue RAS activity). ACE inhibitors have been demonstrated to attenuate left ventricular dilation and improve survival in both patients and experimental models of heart failure. 27-130 ACE inhibition may contribute to this improved prognosis of heart failure via effects on these tissue RAS.

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DISCUSSION

- **Dr. Jay Cohn (Minneapolis, Minnesota):** What is the signal for activation of the tissue renin-angiotensin system? In the myocardium, is it some change in wall forces that is doing this?
- **Dr. Alan Hirsch (Boston, Massachusetts):** I would like to think that a hemodynamic signal underlies such an activation. There are minimal data available regarding

the nature of this signal or its transduction. When the results of multiple investigations are reviewed post hoc, the data suggest that the earliest event that occurs in acute heart failure is an increase in left ventricular filling pressures within the first day, and these pressures subsequently remain elevated. Dr. Drexler has suggested that a few days thereafter, angiotensinogen in the heart is increased. Within the first 4 or 5 days, according to Dr. Anversa, there is already some evidence of cardiac myocyte hypertrophy. While increased ventricular wall stress is temporally associated with cardiac renin-angiotensin system (RAS) activation, sympathetic responses might also contribute to this RAS activation.

Dr. Cohn: We have discussed the nonhomogenous wall stress in the ventricle after an area of the heart is infarcted. The wall that is tethered to the infarct area is placed under much more stress than the distant wall. If there were wall force changes to activate the system, nonhomogenous activation might occur in that muscle tissue. Do you know anything about the distribution of messenger RNA and angiotensinogen?

Dr. Hirsch: Localization of cardiac RAS messenger RNAs in normal and disease states has not yet been performed. However, Drs. Mendelsohn and Jackson and colleagues suggest that they can find increased angiotensin-converting enzyme (ACE) activity, not only in the functional myocytes, but also in the infarcted myocardium and in the collagenous structures of the heart. The fact that there is still enzymatic activity in these structures might be important, since angiotensin II may contribute to interstitial fibrosis, cellular hypertrophy and overall remodeling.

Participant: What stimulates the tissue system in acute myocardial infarction? Is is just wall stress? Have ischemic rat models shown any relation between wall stress and system activation? Can there be other signals?

Dr. Hirsch: As we have discussed, the temporal association of increased wall stress and tissue RAS activation is attractive, but the role of increased adrenergic activity or other neurohormones has not been excluded. These studies have not been performed during concomitant adrenergic blockade or in reserpine-treated animals to determine whether these specific responses can be blocked. Another question is whether ACE inhibition can itself block these responses. Is there an angiotensin II-mediated feedback response? Dr. Schunkert has demonstrated in our laboratory that exogenous angiotensin II can induce renal angiotensinogen expression. As noted, ACE inhibition normalizes the renal angiotensinogen induction associated with chronic experimental heart failure. Thus, we believe that there is likely a contribution of local hormonal feedback control in this system. Control of this system in the heart is less clear at present.

Participant: Where is this increased activity seen in the cardiac tissue?

Dr. Hirsch: As I am sure you are aware, ACE is a fairly ubiquitous enzyme, and it is present in cardiac and vascular myocytes, endothelial cells and the conduction system. Which site is primarily responsible for increased ACE activity is not known; however, both right ventricular and septal ACE increase.

Dr. Robert Cody (Columbus, Ohio): Can we presume from the results of the rat model that, under standard conditions, the renin level is not elevated?

Dr. Hirsch: Yes. In the chronic, compensated state in this model, both plasma renin activity and serum ACE activity are normal.

Participant: In the first study of survival in the captopril-treated infarcted rats by Marc and Janice Pfeffer, weren't serum renin levels elevated?

Dr. Hirsch: To my knowledge, they did not measure either baseline renins or the magnitude of serum ACE inhibition during these survival studies.

Interestingly, the Pfeffers used a dose of 2 g/L of captopril in the drinking water of all their animals. I have administered this dose to Sprague-Dawley rats and found that serum ACE is usually acutely inhibited by approximately 80 to 85%. It is not clear that this dose causes sustained inhibition of circulating ACE during long-term administration. Over the course of a year of treatment, I am convinced that total plasma ACE would probably double or triple.

Dr. Cody: Data from the Pfeffer study and from the SOLVD (Studies of Left Ventricular Dysfunction) trial suggest that in earlier heart failure, when circulating renin levels are minimally increased, some of the favorable effects of ACE inhibitors are through mediation of the tissue effects—in the myocardium, the kidney and the vascular smooth muscle. Is that a fair conclusion?

Dr. Hirsch: This is our hypothesis. As a clinician, as long as I can improve ventricular function, ameliorate symptoms and improve survival, I might not initially focus on tissue ACE effects. However, tissue effects may be particularly important because they will allow us to get some idea of the mechanism of action of ACE inhibitors and how to design better drugs.

Participant: Are the benefits of ACE inhibitors in postmyocardial infarction patients unique to ACE inhibitors?

Participant: Goldman in Tucson compared hydralazine and captopril in terms of reduction of infarct size and showed a difference, which was attributed to venodilation from captopril having an impact on wall stress.

Dr. Cody: If in mild heart failure, the endocrine renin system is minimally activated after myocardial infarction, left ventricular geometric abnormalities can be minimized. This would suggest that under the circumstances, the favorable effects of the ACE inhibitor are at the tissue level. The tissue ACE you are studying is presumably carboxypeptidase B.

Dr. Hirsch: The tissue ACE is the dipeptidyl carboxy-peptidase that may cleave either the terminal 2 amino acids but may also occasionally act as an endopeptidase. In any case, each available assay—high-performance liquid chromatography, radioimmunoassay or spectrophotometry—appears to yield relative results for ACE activity that seem to be comparable.

Dr. Cody: What I am getting at is that perhaps we should just drop the "A" in angiotensin-converting enzyme.

Dr. Hirsch: I agree with you. It may be a misnomer, since angiotensin I metabolism is certainly not its only

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biologic effect.

Dr. Cody: In other words, the "angiotensin-converting enzyme" keeps conjuring up the renin system, and what you are measur ng is a carboxypeptidase. This carboxypeptidase may be blocked by an ACE inhibitor. Tais dissociates the concept of tissue "ACE" being of necess ty related to the endocrine renin system. How do you know that this is not just carboxypeptidase? And that this more generic carbox peptidase helps mediate some of these favorable cellular actions?

Dr. Cohn: The evidence certainly supports the icea that something s happening at the tissue level that cannot be measured systemically. In our model of left ventricular damage in the cog, the early hypertrophy was not associated with a circulating increase in renin activity, but it was inhibited by converting enzyme inhibition, which does not affect blood pressure.

Participant: It is hard to believe that the effect is all hemodynamic or that it is working through a circulating system when the renin system is not activated.

Dr. Hirsch: Nonhypotensive doses of ACE inhibitors have already been shown to alter vascular and cardiac remodeling. These effects clearly appear to be mediated by factors other than plasma angiotensin II, but none of us has yet definitively determined that this mediator is cardiac angiotensin II.

Participant: Can you comment on potential differences between ACE inhibitors and their tissue effects?

Dr. Hirsch: Clearly, each of the many drugs available demonstrate a differing ability to penetrate and bind to

each tissue ACE. We are currently examining this tissue of "equipotent" inhibition in the heart and kidney. I am becoming more convinced that plasma ACE inhibition for available agents will not predict their pharmacodynamic tissue effects.

Dr. Cody: Is there another marker of the tissue renin system that can be measured to get an idea of specificity?

Dr. Hirsch: There are many tools available now, but which is the best? We can measure the messenger RNA for each component and the enzymatic renin or ACE activity, but there is still a need for improved methods for differentiating angiotensin II from angiotensin I and angiotensin III.

Dr. Cody: The implications are that ACE inhibitors might just be the first generic way to get to the important role of carboxypeptidase in cardiovascular medicine.

If one gives an ACE inhibitor, it blocks tissue ACE, and we infer that our observations are therefore extrapolated to the renin system. But it could be that the ACE inhibitors just happen to be the best carboxypeptidase inhibitors that we have. If you give an ACE inhibitor and an angiotensin II antagonist in a model in which plasma renin is not a factor and find that the biologic effects are identical, then you can conclude that the observed response is an effect of blocking the renin system, rather than just a more generic carboxypeptidase effect. This may be the best way to demonstrate in studies such as those which you are conducting, that the observed responses are not a generic carboxypeptidase effect that just happens to be blocked by an ACE inhibitor.

Neuroendocrine Activity in Congestive Heart Failure

Gary S. Francis, MD

The increased neuroendocrine activity in patients with congestive heart failure appears to be a generalized attempt to maintain blood pressure at the expense of reduced cardiac performance and salt and water retention. It is likely that baroreceptor dysfunction contributes to increased sympathetic nervous system activity in patients with congestive heart failure. The usual tonic inhibitory messages emanating from baro- and mechanoreceptors in the great vessels and heart fail to adjust sympathetic traffic from the brain to the periphery, leading to uninhibited sympathetic tone. Arginine vasopressin and plasma renin activity may be increased secondarily; however, plasma renin activity activation could also be induced by a low-salt diet and diuretic use. Preliminary baseline data indicate that patients with left ventricular dysfunction (ejection fraction ≤35%) but no or very mild symptoms of heart failure have increased plasma levels of norepinephrine, atrial natriuretic factor and arginine vasopressin, while plasma renin activity is normal, suggesting that neuroendocrine activity contributes to the pathogenesis of congestive heart failure. Neurohormones such as angiotensin II may alter gene expression, leading to changes in the shape and size of the cell. Remodeling of the heart and blood vessels is associated with both heart failure and hypertension. Angiotensin-converting enzyme inhibitors have been demonstrated to retard or reverse the remodeling process under certain experimental conditions. Studies are currently under way to test this possibility in patients.

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n patients with congestive heart failure, neuroendocrine activity increases in an attempt to maintain blood pressure, even at the expense of increased blood volume and reduced myocardial performance. In the short term, this is achieved by increasing sympathetic drive to the heart and blood vessels, and in the long term by retention of salt and water.² The renin-angiotensin-aldosterone system is activated to support these processes³ and arginine vasopressin (AVP) is released.⁴ Other unidentified or poorly characterized vasoconstrictor substances, such as neuropeptide Y,5 may also be released. As if to counterbalance these vasoconstrictor and sodiumretentive forces, a number of vasodilator and natriuretic substances are released. These include prostaglandin E₂ metabolites,6 dopamine7 and atrial natriuretic factor (ANF).8 Preliminary data also suggest that endotheliumderived relaxation factor activity may be reduced in heart failure,9 which might also contribute to the overall state of enhanced vasoconstriction.

Some data suggest that increased levels of plasma norepinephrine¹⁰ and ANF¹¹ in patients with congestive heart failure are related to survival, the highest levels being associated with the poorest survival rate. Moreover, heightened sympathetic activity, 12 excessive angiotensin II levels¹³ and increased AVP¹⁴ have become therapeutic targets, in some cases with marked success. 13 ANF¹⁵ and competitive inhibitors of its enzymatic degradation¹⁶ are also being explored as potential treatment agents for heart failure. Dopaminergic agonists have been developed, 17 and agents that enhance endogenous prostacycline synthesis (thromboxane synthetase inhibitors) are being intensively studied. The somewhat frenetic pace in the drive to find new treatments for congestive heart failure is based in part on the perception that its incidence is increasing and that it has an unusually high mortality but is responsive to treatment. 13,18,19

Despite the recent interest shown in neuroendocrine factors in heart failure, a number of crucial uncertainties remain to be explored. If neuroendocrine activity represents biologic signals, it remains unclear how these signals are activated; when, in the natural course of left ventricular dysfunction and subsequent heart failure, they are activated; and how processing of the signals influences cellular events, particularly within the left ventricular myocyte and smooth muscle cells. All that is known is that, if a snapshot of neuroendocrine activity in heart failure is taken, it shows increased activity, and a profile describing this activity at one point in time can be drawn. This article discusses how the signals might be activated. when in the natural course of heart failure the neuroendocrine activity begins and how certain signals (norepinephrine and angiotensin II) may possibly interact with the myocardial cell to alter protein synthesis and cell shape.

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PLASMA NOREPINEPHRINE

It has been known for more than 25 years that plasma norepinephrine levels are increased²⁰ and myocardial tissue norepinephrine levels are reduced²¹ in patients with congestive heart failure. Initial interpretation of these responses was that they "may have an important supportive role in such patients."2. This interpretation was based in part on observations²² that interference with the sympathetic nervous system by the administration of guanethidine aggravated the heart failure in some patients in New York Heart Association functional classes III and IV. More recent data have confirmed that plasma norepinephrine is increased in patients with heart failure, 23-25 and, as originally suggested,23 the clinical severity of heart failure is associated with baseline plasma norecinephrine levels.26

Direct microneurographic recordings of peroneal nerve activity have also demonstrated increased central sympathetic activity to skeletal muscle in patients with heart failure.²⁷ It is likely that both increased norepinephrine spillover and reduced clearance of norepinephrine from the plasma contribute to the increased baseline levels found in patients with heart failure. 28 There is a greater augmentation of plasma norepinephrine during exercise in patients with heart failure, in terms of absolute values, than in healthy control subjects, but a relative attenuation of plasma norepinephrine during exercise when expressed as a percentage of maximal oxygen consumption (VO₂ max).²⁹ High levels of synaptic cleft norepinephrine are thought to be responsible for reduced β adrenergic receptor density in the heart through a process of down-regulation or desensitization, 30 contributing to a reduced responsiveness to β -adrenergic agonists.³¹ Despite this, responsiveness to calcium is preserved in the failing heart.32

Recent evidence indicates that down-regulation or desensitization of β -adrenergic receptors in cardiomyopathic hearts is reversible. Heilbrunn et al³³ treated a small group of patients with a β -adrenergic blocker (metoprolol) and showed a significant increase in β -receptor adrenergic density over time, accompanied by an improved responsiveness to dobutamine. It remains to be seen whether treatment with metoprolol or other β blockers will be useful in congestive heart failure.

The cause of the increased spillover of norepinephrine in patients with heart failure is still not clear. Current evidence suggests an abnormality of baroreceptor function, resulting in a disturbance of afferent neural traffic from the heart and great vessels to the central nervous system. This paroreceptor dysfunction, the nature of which is unclear, reduces the usual tonic inhibitory signals responsible for reducing central sympathetic traffic to the periphery.34 The net result is a loss of the usual sympathetic inhibition. As a consequence, central sympathetic traffic is increased to the periphery, including skeletal muscles. This has recently been verified by direct recordings of peroneal nerve traffic.27 The baroreceptor dysfunction appears to reverse after cardiac transplantation.35 Moreover, drugs that sensitize the baroreceptor

apparatus, such as digitalis, have been shown to restore baroreceptor responsiveness in patients with congestive heart failure and to lower sympathetic nervous system activity independent of reflex augmentation of cardiac output.³⁶ Treatment with angiotensin-converting enzyme inhibitors also reverses this baroreceptor dysfunction to some extent.37

Until recently, few data have been available on when, in the natural course of heart failure, the sympathetic nervous system is activated. It is not clear whether it is activated as a consequence of the heart failure syndrome, or whether it is an early event that predates the onset of clinical signs and symptoms. Freliminary baseline data from SOLVD (Studies of Left Ventricular Dysfunction) suggest that plasma norepinephrine levels are increased in patients with left ventricular dysfunction (ejection fraction ≤35%) who do not have signs and symptoms of heart failure requiring digitalis or diuretics. 38 There is a further increment in plasma norepinephrine in patients with overt signs and symptoms of heart failure that require treatment. These data suggest that the sympathetic nervous system is mildly activated early in the syndrome of asymptomatic left ventricular dysfunction. Definite proof of this hypothesis will require sequential measurements in a large population of patients over

It is not known how the presumed long-term increase in norepinephrine at the synaptic cleft alters myocardial cellular events. Specifically, how is the signal processed within the cell and what is the net result of the signal with regard to long-term changes in cell size and shape? Data from isolated neonatal rat myccardial cells indicate that norepinephrine, acting through the α_1 -adrenergic system and using the inositol 1,4,5,-tr phosphate (IP₃) and 1,2diacylglycercl (DAG) pathways, increases the release of intracellular calcium and promotes the expression of certain proto-oncogenes.³⁹ These proto-oncogenes presumably code for a number of different proteins that are important in the growth and development of the cell; these include proteins related to growth factors, growth factor receptors, certain protein kinases, guanine nucleotide regulatory proteins (G proteins) and various DNA site-specific enhancer and promoter proteins responsible for activation of RNA replication. It is possible that increased norepinephrine concentration at the level of the cardiac myocyte is related to the increased cell size (hypertrophy) seen in experimental and clinical congestive heart failure. The exact intracellular events leading to this process, however, have not been elucidated.

PLASMA RENIN ACTIVITY

In patients with congestive heart failure, plasma renin activity is increased to highly variable levels that are related to the state of compensation.⁴⁰ Mechanisms thought to increase plasma renin activity include restriction of sodium in the diet, use of diuretics, a hyponatremic perfusate to the macula densa and reduced baroreceptor activity within the renal vasculature and increased sympathetic activity to the kidney. As with the sympathetic

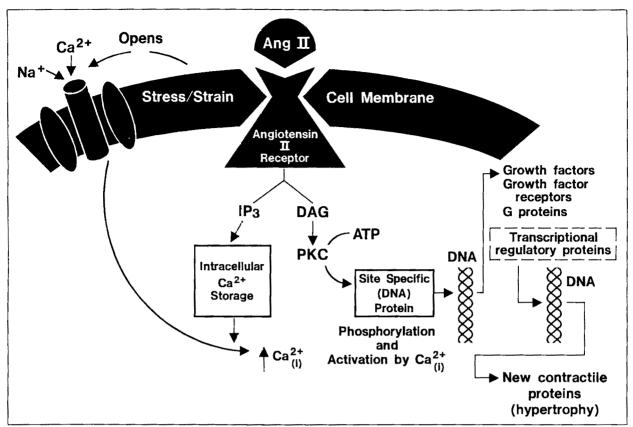


FIGURE 1. Putative mechanism of angiotensin II (AII)-induced growth and development of the cell. All appears to interact with a membrane-bound receptor (still poorly characterized) that activates the inositol 1,4,5-triphosphate (IP₃) and 1,2-diacylglycerol (DAG) pathways. IP₃ releases intracellular calcium [Ca²⁺_(i)], while DAG appears to activate a species of protein kinase C (PKC). Increased intracellular Ca²⁺ and PKC may act together to phosphorylate and thus activate certain DNA site-specific proteins. These DNA site-specific proteins possibly act on DNA as enhancers to initiate RNA polymerase II activity, resulting in an increase in cellular mRNA. New proteins may be synthesized that represent the expression of proto-oncogenes (e.g., c-fos in vascular smooth muscle). Such proteins are likely important in the growth and development of the cell and might include growth factors, growth factor receptors, guanine nucleotide regulatory proteins (G proteins), PKC and other DNA site-specific proteins important in regulating transcription of new contractile proteins. Mechanical forces, such as unusual stresses and strains on the cell membrane, may also alter voltage-dependent Ca²⁺ channels, allowing for enhanced extracellular Ca²⁺ to enter the cell, further augmenting the process of proto-oncogene expression. There may also be other, poorly characterized intracellular AlI receptors, with varying biologic functions.

nervous system, the renin-angiotensin system appears to be activated in an attempt to maintain blood pressure by promotion of peripheral vasoconstriction and retention of salt and water.

Unlike plasma norepinephrine, plasma renin activity is relatively normal (i.e., 1 to 3 ng/ml/hr) in patients with minimally symptomatic or asymptomatic left ventricular dysfunction.³⁸ Most of the increase in plasma renin activity in patients with mild congestive heart failure can be accounted for by diuretic treatment or sodium restriction in their diets. However, patients who are overtly ill with clinical symptoms of heart failure develop marked activation of the renin-angiotensin system.⁴¹

Angiotensin II plays an important role in the growth and development of cells. ⁴² Recent data ⁴³⁻⁴⁵ suggest that angiotensin II acts on a membrane-bound receptor to activate the IP₃ and DAG pathways, leading to increased intracellular calcium and activation of protein kinase C. Protein kinase C then phosphorylates other proteins that

interact with DNA as enhancers or promoters of RNA transcription. The net result in smooth muscle is an increase in c-fos mRNA concentrations.46 These protooncogenes (c-fos, c-myc and others) code for proteins intimately related to cell growth and development. It is also possible that angiotensin II interacts with nuclear receptors independent of the IP3 and DAG pathways. One possible result of these intracellular events is an increase in protein synthesis, including transcription regulatory proteins, contractile proteins (hypertrophy) and growth and development regulatory proteins (hypertrophy). It is also possible that angiotensin II within the tissue intensifies the release of norepinephrine from sympathetic terminals.⁴⁷ Augmented norepinephrine release might further stimulate the expression of proto-oncogenes related to cellular growth and development. Figure 1 depicts a possible schema whereby angiotensin II may stimulate the synthesis of proteins related to cell growth and development.

ATRIAL NATRIURETIC FACTOR

ANF is a peptice that is synthesized and stored in he myocardium and released primarily in response to increased atrial stretch. 48 Other signals can probably initiate the release of stored ANF (e.g., rapid heart rate), and it is likely that both the atria and ventricles can respond to the release stimuli.49 It has been presumed that since increased right atrial pressure is a potent stimulus for the release of ANF, circulating ANF might increase in patients with mildly symptomatic or asymptomatic heart failure, despite the absence of overt signs and symptoms of heart failure. Preliminary baseline data³⁸ substantiate this suggestion. A twofold increment in circulating ANF was found in patients with asymptomatic or mildly symptomatic left ventricular dysfunction. A further increment in circulating ANF levels has been found in patients with overt congestive heart failure. It thus seems likely that ANF is released early in the course of mild congestive heart failure, probably when filling pressures begin to rise but before the appearance of signs or symptoms.

The intracellular activities after ANF stimulation are complex and still not entirely understood. There appear to be at least two different ANF receptors on smooth muscle cells. The ANF₁ receptor is linked to particulate guanylate cyclase and is primarily responsible for the generation of the second messenger cyclic-guanine monophosphate (GMP) from cyclic-guanine triphosphate (GTP). Cyclic-GMP appears to activate a cyclic-GMP kinase, which in turn phosphorylates a specific protein that appears to dephosphorylate the myosin light chain, which in turn leads to relaxation of the smooth muscle cell.⁵⁰ The ANF₂ receptor, which is not linked to particulate guanylate cyclase, may serve a clearance or storage function.51

As with plasma norepinephrine, high plasma ANF levels have been associated with shortened survival in patients with chronic heart failure. 11 However, it is not clear whether high levels of circulating ANF have independent prognostic power or if they are simply markers of other disturbances in circulatory homeostasis and do not directly contribute to a poor prognosis.

ARGININE VASOPRESSIN

A number of laboratories have reported high levels of circulating AVP in patients with congestive heart failure. The precise stimulus for the release of AVP from the posterior rituitary gland is not understood, but appears to be primarily due to nonosmotic factors. As with plasma norepinephrine, it is possible that baroreceptor autonomic dysfunction contributes to heightened AVP levels.²⁴ It is also possible that high circulating levels of angiotensin II stimulate the release of AVP. Many patients with severe heart failure have AVP levels disproportionate to the degree of serum osmolality (i.e., the circulating levels of AVP are higher than expected for the degree of serum

Some baseline data³⁸ indicate that plasma AVP levels are significantly increased in asymptomatic or mildly symptomatic patients with left ventricular dysfunction. A

further increment is found in patients with overt congestive heart failure. Therefore, as with plasma norepinephrine and ANF levels, it appears as though the AVP increases occur early in the natural course of congestive heart failure, before the onset of overt signs and symptoms. One possibility is that the increased AVP is partly in response to the antagonistic effects of ANF on the renal response to AVP (i.e., renal AVP receptors may be blocked by ANF), thus creating the perceived need for higher AVP levels (Steven Goldsmith, personal communication).

The cellular events in the kidney and vascular smooth muscle after stimulation by AVP are complex and not well understood. There appear to be at least 2 types of AVP receptors in the peripheral vasculature that subserve both vasoconstriction and vasodilation.⁵² These receptors appear to be linked to the IP3 and DAG signalprocessing systems. The dominant effect of AVP on the peripheral vasculature is to heighten resistance, but this apparently depends on the regional vascular bed involved and the type of AVP receptor engaged. AVP is also known to have vagotonic effects and perhaps direct negative inotropic properties. Its influence on the kidney is primarily to reduce the clearance of free water and thus maintain a normal osmolality. AVP also appears to have important influences on the brain and other tissues, but these have not been intensively studied. As long as there remains the potential to use AVP antagonists in the treatment of heart failure,53 interest in AVP will persist.

ENDOTHELIAL RELAXATION FACTOR AND **ENDOTHELIN**

Endothelial relaxation factor (EDRF) and endothelin are important peptides that regulate smooth muscle relaxation (EDRF) and contraction (endothelin). Many signals will release EDRF from endothelial cells, including acetylchcline, histamine, thrombin and adenosine triphosphate.⁵⁴ Moreover, changes in blood flow appear to release EDRF.55 EDRF probably is nitric oxide, which activates soluble guanylate cyclase, which in turn is partly responsible for converting GTP to cyclic-GMP. The net result is the dephosphorylation of myosin light chains, which leads to relaxation of smooth muscle cells (an action similar to that of ANF). Recent evidence from an experimental model of heart failure suggests a deficiency of EDRF in congestive heart failure. This is an area of intense research activity, both in the context of congestive heart failure and systemic hypertension.

Endothelin is a recently described peptide⁵⁶ that appears to have at least three different isoforms and is the most potent smooth muscle-contracting substance yet described. It is primarily an autocoid, so that it is synthesized, released and acts locally. Recent preliminary data⁵⁷ indicate that circulating levels of endothelin are increased in hypertensive patients, and unpublished observations incicate that they may also be increased in patients with congestive heart failure (J. C. Burnett, personal communication). Much less is known about the signals that stimulate endothelin release, and its biologic activity on smooth muscle cells is still being investigated.

Endothelin acts on a specific high-affinity receptor, ⁵⁸ and is not an endogenous agonist for voltage-dependent calcium channels, as originally hypothesized. Endothelin appears to act through the IP₃ and DAG pathways, ⁵⁹⁻⁶¹ as do angiotensin II and AVP, but the contraction induced by endothelin is more persistent. ⁶²

CONCLUSIONS

The clinical syndrome of congestive heart failure is characterized by activation of an array of neuroendocrine systems. We are just beginning to understand the signals that stimulate neuroendocrine activity; baroreceptor dysfunction probably makes an important contribution. It appears that some neuroendocrine stimulation, including the sympathetic nervous system, ANF and AVP, occurs early in the natural course of heart failure. Plasma renin. on the contrary, is normal in patients with asymptomatic or mildly symptomatic left ventricular dysfunction, but appears to be subsequently activated in large measure by a sodium-restricted diet and use of diuretics. In advanced heart failure, renin is released by numerous mechanisms, including salt restriction, diuretic treatment, baroreceptor dysfunction, hyponatremic perfusate to the macula densa, reduced renal blood flow and heightened sympathetic activity to the kidney.

Perhaps the most exciting observations concern the potential for angiotensin II and norepinephrine to promote gene expression. Protein synthesis in both cardiac myocytes and smooth muscle cells appears to be enhanced via complex intracellular pathways that are just beginning to be understood. The possible result of this activity is a change in the growth and possibly the shape of the cells. Hypertrophy and remodeling of the cardiac myocyte and vascular smooth muscle that subsequently ensue may be critical events in the development of heart failure and hypertension. Preliminary data from animal models suggest that inhibition of the angiotensin-converting enzyme may retard the hypertrophic process in both heart failure⁶³ and hypertension.⁶⁴ It is possible that treatment with angiotensin-converting enzyme inhibitors will eventually prove useful in the prevention of cellular remodeling, thus changing the natural course of the disease process.

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DISCUSSION

Participant: Dr. Francis, you have shown the effect of angiotensin II on cellular activity in the myocardium and vascular smooth muscle. How does that relate to the other actions of angiotensin II on the kidney or adrenal gland? How do these cellular signals interrelate?

- **Dr. Gary Francis (Minneapolis, Minnesota):** We do not know. We do know that angiotensin II is acting through the IF₃ and DAG pathways, at least with regard to surface membrane receptors. Data now suggest that there may be angiotensin II receptors within the cell, and there is the possibility that angiotensin II may interact indirectly with nuclear receptors. The processing of that signal is not known, nor is it known what the biologic consequence cf it is going to be. These schematograms simply deal with the conventional membrane-bound angiotensin II receptor system.
- **Dr. Karl Swedberg (Gothenburg, Sweden):** What is the effect of angiotensin II activity on, for example, the interstitial myocyte?
- Dr. Francis: There is growing interest in the interstitum. The genes that code for collagen have not been clearly identified, and we do not know what the signals are. There does appear to be a temporal discordance between the increase in the size of the myocyte and the increase in collagen tissue. Early on, there is an increase in the collagen type that has poor tensile strength. Later the myocyte itself tends to increase in size. The last thing that happens is that there are increases in the thick collagen fibers of great tensile strength. Whatever the signal is, the response to the signal seems to be at least temporally dissociated between the collagen and the myocyte, which would suggest that different processes are probably involved.
- **Dr. Swedierg:** If you wanted to measure neuroendocrine activation, which hormones would you study?
- **Dr. Francis:** Our own experience has been that norepinephrine provides the most important prognostic information. In tracking these neurohormones sequentially, there is more "noise" in the rerin activity, which seems to vary enormously, depending on the clinical status of the patient. Of course, recently, all patients seem to be receiving angiotensin-converting enzyme (ACE) inhibitors, so I no longer know how to interpret the data.
- Dr. Jay Cohn Minneapolis, Minnesota): The correlation between plasma renin and norepinephrine in heart failure is so poor that it is obvious that the renin system is responding to something else. It has been our contention, based on the response to vasodilators, that the baroreceptor in the kidney remains functional in heart failure, and

that as the blood pressure decreases, the renin level increases because of the intrarenal baroreceptor mechanism. In contrast, the carotid/aortic baroreceptor response is inhibited, so norepinephrine will not rise, but renin will. I think the renin system is responding independently of the sympathetic nervous system at this stage. Norepinephrine is probably the most sensitive marker of early neurohormonal activation, and it would be surprising to see atrial natriuretic peptide (ANP), renin or atrial natriuretic factor (ANF) stimulated without the sympathetic nervous system being stimulated first.

Participant: We know that if a patient is given a diuretic and the atrial pressure decreases, ANP levels should also decline. This is not true with norepinephrine. In a stable patient with heart failure given diuretics, the norepinephrine level remains elevated.

Participant: Is that good or bad in terms of prognosis? Participant: My belief is that diuretics do not change the prognosis, but do change ANF levels, which would make me suspect that ANF in a treated patient is not a valuable guide to prognosis.

Response to Stress

Dr. Swedberg: Should we stress the system more frequently and measure neuroendocrine activation?

Dr. Cohn: Exercise, tilt and vasodilators are all stresses to the system, and these have been studied. Dr. Francis, do we know whether the patient with heart failure has a diminished or an enhanced response to exercise in terms of the sympathetic nervous system?

Dr. Francis: It depends on how the data are analyzed. You can stress these systems, and many patients will respond. I am convinced that the lack of response gives us predictive information about a patient. If you vasodilate, tilt or exercise the patient, and he or she is unable to mount much of a neurohormone response, that portends a poor prognosis for the patient.

Participant: One study that needs to be done is to look sequentially at treatment to determine whether it symptomatically improves the response of the neurohormonal system to the stress, and whether that is prognostic.

Dr. Robert Cody (Columbus, Ohio): In a paper we published in *Circulation* (Cody et al. 1982;66:135–141), which was actually one of the first studies of an angiotensin-converting enzyme (ACE) inhibitor in patients with

heart failure, we looked at responses to tilt, cold pressor tests and Valsalva maneuver at baseline and after 2 months of captopril therapy, and showed that the sympathetic responses (and parasympathetic, too, in terms of the Valsalva maneuver) did improve with ACE inhibitor treatment. In other words, the magnitude of heart rate and blood pressure response to cold pressor test was much more like normal after 2 months of ACE inhibition than it was at baseline. The response to the Valsalva maneuver tended to normalize after 2 months, and the heart rate response to tilt improved. At the time, I thought it was stretching a point to say that these were direct effects of ACE inhibitors, rather than effects of treating the heart failure. But there is increasing evidence to suggest that there is an ACE inhibitor effect, that is, a direct effect of blocking angiotensin II. On presynaptic release of norepinephrine, there are also some data to suggest that β receptor density on lymphocytes changes during treatment with ACE inhibitors.

Dr. Cohn: My concern is that if you condition patients with heart failure, their plasma norepinephrine levels decline, and I would suspect that their reflex responsiveness would also improve. We do not know how much of what we are seeing is secondary to just giving a sedentary person a treatment that makes him or her feel better; he or she becomes more active and consequently normal reflexes are restored. The response may not relate directly to the therapy used.

Baroreceptor Activity

Participant: Dr. Francis suggested that baroreceptor activity is the most likely signal that triggers the neurohormones. Do we know which baroreceptors are responsible for activating the renin-angiotensin system?

Dr. Alan Hirsch (Boston, Massachusetts): The answer is complex. There is no question that both animal models and patients with heart failure demonstrate blunted responses to changes in cardiopulmonary baroreceptor loading conditions. Similar changes in arterial baroreceptor function have also been noted. The failing heart has a less responsive afferent sensing system and may not appropriately inhibit medullary sympathetic outflow. Finally, end-organ responses such as heart rate or forearm vasoconstriction may also be blunted with severe heart failure.

Effects of Enalapril and Neuroendocrine Activation on Prognosis in Severe Congestive Heart Failure (Follow-Up of the CONSENSUS Trial)

Karl Swedberg, MD, Peter Eneroth, MD, John Kjekshus, MD, and Steve Snapinn, PhD, for the CONSENSUS Trial Study Group

This study enrolled 253 patients with severe heart failure (New York Heart Association functional class IV) from 35 centers in Scandinavia, randomly assigned to treatment with placebo or enalapril, in addition to their usual treatment for heart failure. After an initial titration period, the daily doses of enalapril ranged from 2.5 to 40 mg. At the end of the trial, 46% of the placebo-treated patients and 61% of the emalapril-treated patients were alive (p = 0.003); the survival figures at 8 months after completion of the trial were 32 and 48%, respectively (p = 0.001); and 21 and 30%, respectively (p = 0.006) at the 2-year follow-up. In the placebo group, there was a significant positive association between mortality and baseline levels of norepinephrine, epimephrine, angiotensin II, aldosteron≥ and atrial natriuretic peptide; no such association was found in the enalapril-treated patients. The results suggest that the effects of enalapril on mortality are related to a counteraction of the neuroendocrine activation in general and to the renin-angictensin system in particular.

(Am J Cardiol 1990;66:40D-45D)

The poor long-term prognosis for patients with severe congestive heart failure is related to myocardial function, but the reason for the progressive myocardial deterioration observed in some patients is not demonstrated by indices of systolic myocardial function. Intramyocardial structural or metabolic changes are probably important, and compensatory systems, such as the sympathetic and renin-angiotensin systems, could also have adverse effects on prognosis. In order to improve prognosis, treatments should directly or indirectly affect these adverse compensatory mechanisms. We have previously reported beneficial effects of treatment with β -adrenergic blockers in idiopathic dilated cardiomyopathy.

The CONSENSUS trial⁴ demonstrated a clear reduction in mortality among patients with severe congestive heart failure after the addition of the angiotensin-converting enzyme (ACE) inhibitor enalapril. We have recently reported data on neuroendocrine activation in these patients.⁵ In this article, we report further prognostic relations with neuroendocrine activation observed in the CONSENSUS trial.

MATERIALS AND METHODS

The study design and inclusion criteria have been reported previously.⁴ At 35 centers in Scandinavia, 253 patients with severe heart failure (New York Heart Association functional class IV) were randomly assigned to placebo (n = 126) or enalapril (n = 127), in addition to their conventional treatment for heart failure. All patients were receiving diuretics (the mean daily furosemide dose was 210 mg., 94% were receiving digitalis, and 50% vasodilators (except ACE inhibitors). After initial titration, the dose of enalapril ranged from 2.5 to 40 mg daily. The 6-month mortality, calculated from life-table analysis, was 48% in the placebo group and 29% in the enalapril group. At the end of the trial (December 15, 1986), open therapy with enalapril was recommended for all patients.

Blood samples: Blood samples for baseline assessment of hormone levels were drawn from the patients after they had rested for 30 minutes in the supine position. Blood samples were not obtained from 14 patients for various reasons. The overall results have been presented elsewhere.⁵

Hormone analysis: All hormone concentrations were determined at the same laboratory, and samples from

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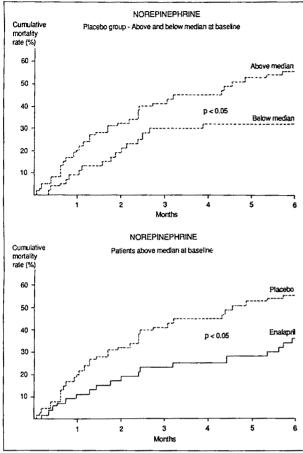


FIGURE 1. Mortality in the placebo-treated patients with baseline norepinephrine levels above and below the median and in placebo- and enalapril-treated patients with baseline norephinephrine levels above the median (p <0.001 in the placebo group).

each patient were analyzed in one assay. Analyses could not be conducted for every patient because of lack of sufficient amounts of blood.

Norepinephrine and epinephrine were measured in EDTA-plasma by a radioenzymatic method, using kits from Amersham UK. The intra- and interassay coefficients of variation were below 19 and 31%, respectively. Reference values in the laboratory were 484 ± 318 pg/ml for norepinephrine and 132 ± 112 pg/ml for epinephrine. The median values were 462 and 126 pg/ml, respectively.

Aldosterone was measured by radioimmunoassay according to the procedure described by Walsh et al, 7 using kits from Diagnostic Products Corp. (Los Angeles, California). Cross-reactions with related steroids were negligible (e.g., 18-hydroxycorticosterone, <0.05%; cortisol, <0.005%; and spironolactone, <0.08%). Intra- and interassay coefficients of variation were 7 and 10%, respectively. The laboratory reference value was 404 \pm 208 pmol/L; median, 363 pmol/L (1 ng/dl = 27.8 pmol/L).

Angiotensin II in EDTA-plasma was measured by radioimmunoassay as described by Nussberger et al,8 with kits from Buhlman Laboratories AB (Basel, Switzerland). The intra- and interassay coefficients of varia-

tion were 9 and 14%, respectively. The laboratory reference value was 20 ± 7 pg/ml (median, 16 pg/ml).

ACE activity was determined in serum by a radioenzymatic method, 9,10 using kits from Buhlman Laboratories. 11 The intra- and interassay coefficients of variation were 6 and 8%, respectively. The laboratory reference value was 25 ± 12 U/min · L (median, 28 U/min · L).

Atrial natriuretic peptide (ANP) in EDTA-plasma was measured by radioimmunoassay with kits from Immunotechnology Service (Wycken, The Netherlands), as previously described. ¹² Intra- and interassay coefficients of variation were 8 and 13%, respectively. The laboratory reference value was 57 ± 21 pg/ml (median, 47 pg/ml).

Follow-up: A questionnaire was distributed twice to all investigators asking about the survival status of all patients at 8 months and 2 years after the conclusion of the CONSENSUS trial, on December 15, 1986.

Statistical methods: The relation between hormone levels and mortality was tested with logistic regression models using continuous hormone values. The log-rank test was used to compare the mortality experiences of the two treatment groups and for subgroups of patients according to baseline hormone levels. The follow-up data

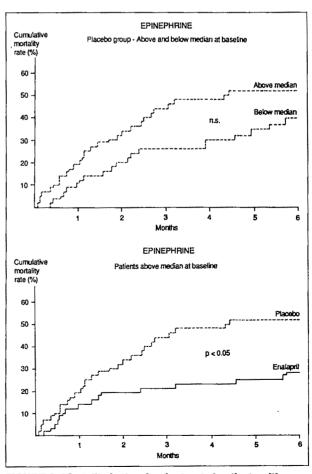


FIGURE 2. Mortality in the placebo-treated patients with baseline epinephrine levels above and below the median and in placebo- and enalapril-treated patients with baseline epinephrine levels above the median (p = 0.001 in the placebo group).

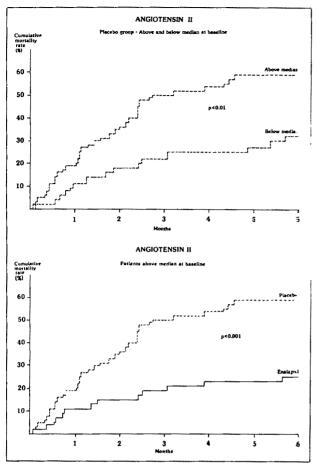


FIGURE 3. Mortality in the placebo-treated patients with baseline angiotensin II levels above and below the median and in placebo- and enalapril-treated patients with baseline angiotensin II levels above the median (p <0.05 in the placebo group).

were calculated according to life-table techniques.¹³ In the long-term follow-up, the fact that the code was broken at the end of the trial was ignored.

RESULTS

Figures 1 to 5 show that in the placebo group there was a significant positive relation between mertality and baseline levels of norepinephrine (p <0.001), epinephrine (p = 0.002), angiotensin II (p <0.05), aldosterone (p = 0.002) and ANP (p = 0.003). The highest mortality was observed in patients with the highest hormone levels (quartile 4): mertality ranged from 57% (aldosterone to 68% (ANP) in quartile 4. No relation between hormone levels and mortality was found in the enalapril group; the reduction in mortality from placebo to enalapril treatment was consistently largest in quartile 4, ranging from -50% (ANP) to -67% (aldosterone).

Figure 6 shows mortality in the placebo and enalabril groups by baseline hormone levels of norepinephrine (there were about 58 patients in each quartile). For the placebo group, patients with hormone levels above the median had significantly higher mortality than patients with hormone levels below the median. The same consis-

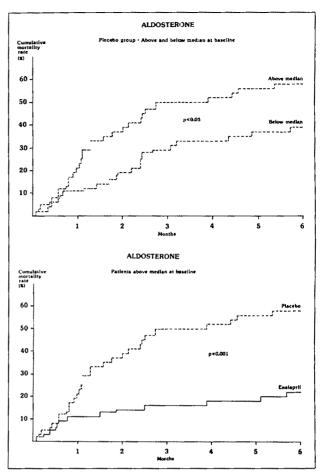


FIGURE 4. Mortality in the placebo-treated patients with baseline aldosterone levels above and below the median and in placebo- and emalapril-treated patients with baseline aldosterone levels above the median (p = 0.002 in the placebo group).

tent pattern was observed for epinephrine, angiotensin II, aldosterone and ANP.

Serum electrolyte and creatinine levels were also compared in the two groups (Figures 7 to 9). Patients with low sodium or high creatinine levels had significantly higher mortality, and their prognoses were significantly improved by enalapril.

Follow-up: During follow-up, approximately 80% of patients in both groups were openly treated with enalapril. The proportions of patients surviving at the end of the trial were 46% of 126 in the placebo group and 61% of 127 in the enalapril group (p = 0.003); at the 8-month follow-up, 32% of the placebo group and 48% of the enalapril group (p = 0.001); and at the 2-year follow-up, 21% of the placebo group and 30% of the enalapril group (p = 0.006).

DISCUSSION

The results of the present trial confirm the observation of Cohn et al¹³ that norepinephrine levels are a guide to prognosis in patients with severe heart failure not treated with an ACE inhibitor. They also support the findings of Gottlieb et al¹⁴ of an increase in ANP levels as a marker of increased mortality. We were also able to demonstrate

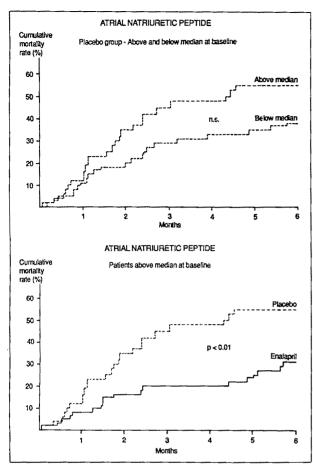


FIGURE 5. Mortality in the placebo-treated patients with baseline atrial natriuretic peptide levels above and below the median and in placebo- and enalapril-treated patients with baseline atrial natriuretic peptide levels above the median (p = 0.003 in the placebo group).

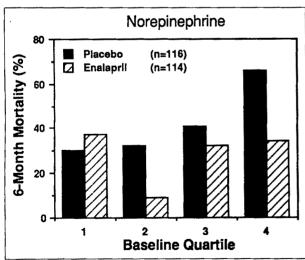


FIGURE 6. Mortality in the placebo- and enalapril-treated patients, by baseline norepinephrine levels expressed in quar-

the same pattern for epinephrine, angiotensin II and aldosterone.

Lee and Packer¹⁵ have reported a positive association between hyponatremia and survival in patients with se-

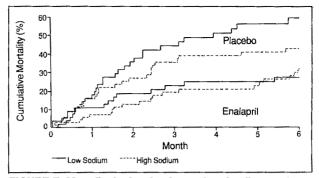


FIGURE 7. Mortality in the placebo- and enalapril-treated patients with baseline serum sodium levels below and above the median (138 mmol/L) (enalapril versus placebo group, low, p = 0.004; high, p = 0.13).

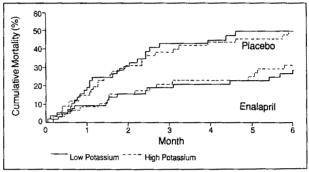


FIGURE 8. Mortality in the placebo- and enalapril-treated patients with baseline serum potassium levels below and above the median (4.1 mmol/L) (enalapril versus placebo group, low, p=0.03; high, p=0.005).

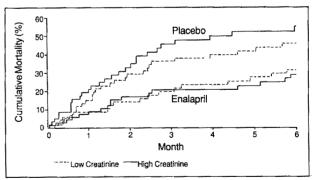


FIGURE 9. Mortality in the placebo- and enalapril-treated patients with baseline serum creatinine levels below and above the median (123 μ mol/L) (enalapril versus placebo group, low, p = 0.10; high, p = 0.004).

vere chronic heart failure. Our data support their observations. The hyponatremic patients had a significantly higher mortality, and patients with serum creatinine levels above the median had a higher mortality, which was significantly decreased by enalapril. This finding is in contrast to that of Packer et al¹⁶ who reported a deterioration in renal function in patients treated with enalapril. However, we used lower enalapril doses titrated to an optimal level starting at 2.5 mg daily, whereas they used a fixed regimen of 20 mg twice a day (40 mg daily).

A SYMPOSIUM: ACE INHIBITION IN CONGESTIVE HEART FAILURE

The variations in neuroendocrine activation observed in our patients could have several explanations. Hemocynamic status is probably important because of the patients' need for compensatory activation of periphecal vascular mechanisms to maintain organ perfusion. The intensity of the treatment may also play a role. Diuretics increase plasma renin levels in previously untreated patients with heart failure. The since all our patients were receiving diuretics, it is not possible to determine their effects on neuroendocrine activation.

We were only able to assess the effects of enalapril on 6-month mortality in patients with pronounced activation of the neuroendocrine systems. The effects in patients with less activation cannot be evaluated from our data because of the small sample size.

Neurohumoral activation may unfavorably affect the clinical status of patients with heart failure by lowering cardiac performance, causing sodium retention and potassium depletion and reducing the capacity of the peripheral vessels to dilate during exercise. Benalapril has been shown to have beneficial effects on symptomatology in heart failure, but it is not clear whether this effect is related to plasma neuroendocrine hormone levels. The beneficial effects of enalapril on mortality were seen for at least 2 years from randomization. This was true in spite of a large crossover to open enalapril after the end of blind therapy. The effects beyond 2 years are unclear from this trial.

CONCLUSION

There is a marked but variable neuroendocrine act vation in severe heart failure, and we demonstrated a significant relation between this activation and mortality among the placebo-treated patients. Mortality was reduced by enalapril, primarily in patients with the most marked neuroendocrine activation. The results suggest that the reduction in mortality correlates with the inhibition of neuroendocrine activation and of the renin-angiotensin system in particular.

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DISCUSSION

- **Dr. Robert Cody (Columbus, Ohio):** Dr. Swedberg, you reported that the patients with the highest serum creatinine levels had the best response to enalapril. What was their median creatinine level?
- **Dr. Karl Swedberg (Gothenburg, Sweden):** The median serum creatinine level was 123 μ mol/L (1.4 mg/dl). In the early part of the trial, patients with serum creatinine levels above 255 μ mol/L (2.5 mg/dl) were excluded; this was later raised to 300 μ mol/L (3.3 mg/dl). Patients were withdrawn if their serum creatinine levels increased to more than 300 μ mol/L (3.3 mg/dl).
- **Participant:** The median creatinine level is very good for 70-year-old patients with class IV heart failure.
- **Dr. Sweiberg:** Yes, but it does not tell you much about the patients' actual renal function. Increased serum creatinine levels in 75-year-old patients indicate poor renal function.
- **Dr. Gary Francis (Minneapolis, Minnesota):** It is remarkable that the mean creatinine level was so low in this aging population. It is also intriguing that the systolic blood pressure in these very sick patients averaged 120 mm Hg.
- **Dr. Swedberg:** I agree; I would have expected the patients to have lower blood pressures. However, these patients had a very high mortality. Systolic blood pressure was significantly related to the combined activation of all the hormones. Patients with more activated neuroendocrine systems had lower blood pressures, but the difference was not marked. It is possible that, because of investigator bias, patients with low pressures were excluded from the study.
- **Dr. Cody:** I wonder if there was also an age effect. The patients had a mean age of 70, which suggests that a number of them were well into their seventies, or even older.
- **Dr. Swedberg:** I want to emphasize that this is the profile of the heart failure population in the community; they are older.

Participant: One criticism of many clinical trials is that they exclude older patients, so we do not have much data on them. The downside, of course, is the older they are, the more likely they are to die.

Participant: You report classifying your patients into quartiles, which raises a sensitive question, and that is the possibility of a beta error. If you study the relationship between treatment response and low quartiles versus high quartiles on many of these factors, you have a very low power to detect a difference.

Dr. Swedberg: I agree that the statistical power is low for subgroups, and particularly for subgroups with mortality below median levels. That is why we let the data tell us where to make the separation. We only used quartiles or medians and no arbitrary divisions or values taken from other trials. Moreover, in the statistical tests, we used continuous variables when the association between hormone levels and mortality in the two treatment groups were compared. It is also important to look at the whole picture, and our findings were consistent with those of previous studies.

Participant: Were there any differences in duration of hospitalization?

Dr. Swedberg: The problem here, of course, is that so many more patients in the placebo group died, that the total hospital days are greater in the enalapril group. If you calculate hospitalizations per patient-year observed, there was a significant reduction in the hospital stay among the treated patients. An important aspect in any mortality trial is that the groups become unbalanced immediately; it is difficult to evaluate any nonmortality end point in a trial with so many deaths.

Participant: You have raised an important concern about the interpretation of data. The data on the quartiles you present almost lead to the conclusion that enalapril has an adverse effect in the low neurohormone group, which might encourage people to use the neurohormones as a marker for patients that should be treated. The danger is that at these low neurohormonal levels, we are dealing with such a low-risk group that you have no power to measure efficacy. If you are designing a study to assess treatment efficacy, it would be far more effective to exclude the low-risk patients according to their neurohormonal levels. If you want to study mortality, you look at the high-risk group and forget the low-risk patients. I am not sure that we shall ever have a data base large enough

to evaluate mortality in the low-risk group.

Dr. Jay Cohn (Minneapolis, Minnesota): Of course, people will say, "If you have to study 10,000 people to find a treatment effect, it must be a very small effect." Is it worth treating 10,000 people with enalapril in order to save a few lives?

Dr. Swedberg: We use indications like that in hypertension treatment.

Dr. Cohn: Yes, but that is being questioned now. The days of identifying persons with a diastolic pressure greater than 90 mm Hg and giving drugs to all of them are probably over. No one has even suggested that the quality of life of a hypertensive patient is improved by lowering blood pressure. We believe the quality of life is being improved with ACE inhibition therapy in patients with heart failure, but the traditional view of antihypertensive therapy is that you cannot make an asymptomatic person feel better. All you can do is prolong life, and if you are not prolonging life, then why treat these asymptomatic people?

Dr. Alan Hirsch (Boston, Massachusetts): An associated question concerns the appropriate use of β -blockers after myocardial infarction. Are we in fact treating large numbers of these patients to achieve the expected decrease in long-term mortality?

Dr. Swedberg: It is a very cost-effective treatment, much more cost-effective than the treatment of moderate hypertension.

Participant: Dr. Swedberg, what are the implications of your findings?

Dr. Swedberg: The interesting question is why the neuroendocrine system is activated in heart failure. It seems unrelated to the symptomatology, which is surprising since the symptomatology is closely related to the hemodynamic derangement. Another interesting finding was that the counteraction of the neuroendocrine activation was closely related to survival. It seems to be important to expose patients to even a small dose of enalapril, because 20% of them received 5 mg or less a day. We do not know the optimal dose, but we do know that even this small dose in heart failure patients will lower plasma ACE levels significantly. I conclude that our data support the notion that is is the actual ACE inhibition, and not merely the unloading, that is important, because ACE inhibition so consistently reduced neuroendocrine activation and mortality.

The American American Journal of Cardiology

OCTOBER 16, 1990

A Symposium: Technetium-99m Myocardial Perfusion Imaging Agents and Their Relation to Thallium-201

GUEST EDITOR:

Daniel S. Berman, MD

Professor of Medicine
UCLA School of Medicine
Director of Nuclear Cardiology
Cedars-Sinai Medical Center
Los Angeles, California

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Introduction—Technetium-99m Myocardial Perfusion Imaging Agents and Their Relation to Thallium-201

Daniel S. Berman, MD

lthough thallium-201 (Tl-201) has excellent physiologic characteristics for imaging myocardial perfusion and viability, its low energy (68 to 80 keV) is suboptimal for scintillation camera imaging, and its relatively long half-life (73 hours) results in suboptimal radiation dosimetry. To circumvent these limitations, investigators have attempted for over a decade to develop a myocardial perfusion agent labeled with technetium-99m (Tc-99m), a tracer with ideal physical properties for scintillation camera imaging (monoenergetic gamma of 140 keV and 6-hour half-life). This search met with success in 1982, when the group at the Peter Bent Brigham Hospital announced the development of Tc-99m isonitriles. In the experimental animal, the myocardial uptake of these agents was shown to be proportional to the regional myocardial blood flow. More recently, another group of Tc-99m-labeled tracers, called boronic acid adducts of technetium dioximes (BATO compounds), were demonstrated to have high myocardial extraction with subsequent myocardial concentration also proportional to regional perfusion.2 As of 1990, radiopharmaceuticals from both of these classes have been submitted to the Food and Drug Administration for approval, offering the promise that in the near future they will be available for routine clinical use.

TECHNETIUM-99m-LABELED ISONITRILES

Of multiple Tc-99m-labeled isonitrile compounds, 3 have been applied clinically. All 3 have similarly avid myocardial uptake. The first, Tc-99m-t-butyl isonitrile (TBI), was suboptimal for myocardial imaging due to its prominent hepatic and pulmonary uptake. ³⁻⁶ Persistent liver uptake of TBI frequently obscured defects in the inferior left ventricular wall. In addition to further obscuring myocardial defects, pulmonary TBI could behave as a reservoir of the tracer. With the subsequent washout of the tracer from the lungs, a significant amount could

be delivered to the myocardium and alter the resulting perfusion pattern from that corresponding to the initial injection and uptake of TBI. The second tracer, Tc-99m carboxyisopropyl isonitrile (CPI), demonstrated progressive hepatic accumulation over time despite excellent myocardial uptake and also relatively rapid washout from the myocardium.^{6,7} The third, Tc-99m methoxyisobutyl isonitrile, known generically as Tc-99m sestamibi, has emerged as the isonitrile with the most favorable biologic characteristics for myocardial perfusion imaging.⁸ Unlike TBI and CPI, Tc-99m sestamibi has only transient hepatic uptake with prompt hepatobiliary excretion and minimal lung uptake.⁹

Tc-99m sestamibi is distributed in the myocardium in proportion to blood flow in a manner parallel to that observed with Tl-201 (i.e., with a decrease of extraction at very high flow rates), although with a somewhat lower myocardial extraction fraction. Of importance, in contrast to Tl-201, there is minimal myocardial redistribution of Tc-99m sestamibi over time. The combination of transient early hepatic uptake and minimal myocardial redistribution makes 30 to 60 minutes after injection the ideal imaging time for Tc-99m sestamibi. The minimal redistribution allows uncoupling of the time of injection and the time of imaging, which is important for applica-



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tions in acute myocardial infarction. In addition, this property makes Tc-99m sestamibi ideal for single photon emission computed tomography (SPECT) imaging, with its prolonged acquisition time.

BORONIC ACID ADDUCTS OF TECHNETIUM **DIOXIME COMPOUNDS**

The BATO compounds, which form the other class of Tc-99m myocardial perfusion agents, are neutral lipophilic complexes of boronic acid. The agent from this class that has been developed commercially is Tc-99m teboroxime. 11,12 Unlike Tc-99m sestamibi, which is less efficiently extracted than Tl-201, Tc-99m teboroxime is extracted with greater efficiency than Tl-201 throughout a broad range of flow rates. 12 Tc-99m teboroxime's myocardial uptake is rapid, with excellent myocardial visualization 2 minutes after injection. The myocardial clearance, however, is also rapid, with biexponential clearance half-times of 2 minutes (68%) and 78 minutes (32%). These properties necessitate the confipletion of imaging within 15 to 20 minutes from the time of injection. Since tomographic acquisition with the standard single detector cameras typically requires prolonged imaging times, this agent is not ideally suited for SPECT imaging. Another limitation is the persistent hepatic accumulation of the tracer; its liver residence half-time is approximately 1.5 hours. This hepatic uptake occasionally interferes with inferior wall visualization.

SYMPOSIUM ON TECHNETIUM-99m AGENTS

These new myocardial imaging agents have distinct physical properties from Tl-201 and distinct biologic properties from each other. Soon after the introduction of these tracers, it became clear that new acquisition, processing, display and quantitation protocols would have to be developed to optimize their use. Furthermore, the ways in which these new agents differ from Tl-201 and from each other provide an opportunity to explore new methods for using the agents (e.g., gated SPECT with Tc-99m sestamibi) and new clinical settings in which they may be applied (e.g., before and after thrombolytic therapy with Tc-99m sestamibi). Thus, to explore the issues posed by the new tracers, a symposium on Tc-99m myocardial perfusion imaging agents and their relation to Tl-201 was held February 22 to 25, 1990, in Palm Beach, Florida. Participating in the symposium were many of the foremost researchers in myocardial imaging from the United States, Canada and Europe.

The symposium was unique is several ways. First, it brought nuclear cardiologists together with specialists from both nuclear medicine and nuclear radiology. This kind of collaboration is essential to the successful development of myocardial imaging techniques and procedures. Second, the level of experience and expertise of those attending the meeting was unusually high. On average, attendees reported spending 57% of their time on nuclear cardiology procedures, and 61% of the audience reported performing ≥7 thallium studies/day. Third, the meeting involved experts not only from the United States, but also

from Canada and Europe, providing an opportunity to call on the extensive experience with the newer imaging agents that has been gained outside the United States.

An important goal of the meeting was to bring together a wide variety of viewpoints on myocardial imaging agents and procedures from experts of diverse geographic, clinical and scientific backgrounds. By the choice of speakers and participants and in the amount of time allowed for discussion, the aim was to foster the exchange of ideas, experience and opinion. This supplement was developed from the presentations of the symposium, and is thus a distillation of the most current information available on Tc-99m imaging agents.

The reports in this symposium are divided into 5 sections. In the section on experimental studies of the basic properties of the Tc-99m imaging agents, Beller and Sinusas summarize current animal studies of Tc-99m sestamibi in comparison to Tl-201. These studies demonstrate that the uptake of Tc-99m sestamibi is proportional to blood flow to viable myocardium. Meerdink and Leppo then compare the physiologic properties of Tc-99m sestamibi and Tc-99m teboroxime to Tl-201. Their report deals primarily with elegant studies in isolated perfused rabbit hearts that result in calculations of tissue extraction, retention and capillary permeability of the tracers. Their report also provides a detailed description of their methodology, derived from the work of Bassingthwaighte. In addition, they describe results of subcellular fractionations and cell culture experiments. Their work clearly demonstrates that Tc-99m sestamibi, Tc-99m teboroxime and Tl-201 all have very different cardiac transport mechanisms. The investigators summarize by stating that all tracers show adequate transport characteristics for perfusion imaging, but that differences in transport and retention will require the development of different types of clinical imaging protocols, and may result in different clinical uses.

The second section deals with acquisition, processing, quantitation and technical considerations, with particular focus on Tc-99m sestamibi imaging. Smith and Watson discuss the optimization of planar imaging for Tc-99m sestamibi. Their report presents many new developments that have been specifically tailored to Tc-99m sestamibi, including image standardization, placement of regions of interest, a new background subtraction, rescaling of images, image registration, quantitation of "rest redistribution" or defect reversibility, gated acquisition and dualisotope (Tc-99m sestamibi and Tl-201) acquisitions.

Garcia and associates then discuss recent advances in technical aspects of myocardial SPECT imaging with Tc-99m sestamibi. In this report, the investigators describe optimization of the technical aspects of Tc-99m sestamibi SPECT with respect to radiopharmaceutical doses, imaging sequences, acquisition parameters, reconstruction filters, perfusion quantification methods and multidimensional methods for visualizing perfusion distribution. The report describes theoretical considerations, phantom studies and preliminary patient results that have led to optimized protocols developed at Emory University and Cedars-Sinai Medical Center for same-day rest-stress studies. The investigators discuss a wide variety of improvements over current Tl-201 quantitative methodologies that are being developed for Tc-99m sestamibi SPECT to take advantage of its ideal physical and biologic characteristics for SPECT imaging.

The third section of the symposium addresses the use of Tc-99m in acute coronary artery disease. Boucher describes results reported to date with respect to detection and localization of myocardial infarction using Tc-99m sestamibi imaging at rest. These results include those of a large multicenter trial that demonstrated a very high rate of detection of perfusion abnormalities by Tc-99m sestamibi in patients with myocardial infarction, and a very low frequency of perfusion defects in normal subjects. In addition, Boucher reports the results of studies from his laboratory assessing the relation of perfusion defects at rest to severe coronary stenosis, and evaluating the relation of Tc-99m sestamibi uptake to clinical markers of myocardial viability.

Wackers reviews the use of Tc-99m sestamibi to assess the efficacy of thrombolytic therapy for acute myocardial infarction. This report presents the results of several studies that have demonstrated that Tc-99m sestamibi given before and after thrombolytic therapy can indicate the area at risk as well as the degree of myocardial salvage. Wackers also describes how these studies can be used to document successful reperfusion, and discusses several different approaches in which Tc-99m sestamibi may play an important clinical role in the assessment of the patient undergoing thrombolytic therapy, including the potential of using an early postthrombolytic therapy study alone (not requiring a prethrombolysis injection) to aid in selection of patients for early angiography.

Grégoire and Théroux then report an interesting study of patients with unstable angina, comparing Tc-99m sestamibi SPECT and 12-lead electrocardiography. They demonstrate that when injected during an episode of chest pain, Tc-99m sestamibi has high sensitivity and specificity for detection of significant coronary artery disease. They also show that when a subsequent injection during a pain-free interval demonstrates a smaller perfusion defect, the specificity for coronary artery disease increases. They report clear improvement in sensitivity and specificity for coronary artery disease, compared to the resting electrocardiogram, in unstable angina patients. This novel approach may lead to an important new application of myocardial perfusion imaging, less feasible with TI-201 due to its potential for redistribution before the performance of SPECT imaging.

The fourth section deals with the results of clinical trials of the Tc-99m agents in chronic coronary artery disease. Maisey and associates describe the results of planar imaging techniques. They demonstrate that in several large trials Tc-99m sestamibi has shown sensitivity and specificity for coronary artery disease similar to that of Tl-201 planar imaging. They report that end-diastolic perfusion imaging appears to improve the concordance between Tc-99m sestamibi and angiography. They de-

scribe a method of assessing regional and global left ventricular function, and also address the functional implications of elevated lung and right ventricular uptake of Tc-99m sestamibi.

Maddahi and associates describe the results of multiple trials using Tc-99m sestamibi SPECT in the evaluation of chronic coronary artery disease. In preliminary reports of a large multicenter North American clinical trial, the investigators show that protocols using acquisition parameters essentially the same as those used for Tl-201 SPECT resulted in similar findings between Tl-201 and Tc-99m sestamibi for presence and type of perfusion defects and for detection of coronary artery disease. The investigators also describe preliminary observations with respect to perfusion defect intensity, suggesting equal intensity of defects with SPECT imaging using Tc-99m sestamibi and Til-201 but less intense (less pronounced) defects with planar imaging with Tc-99m sestamibi compared to Tl-201. These findings suggest that SPECT may be even more important with Tc-99m sestamibi imaging than it has been with Tl-201. Results of preliminary approaches for quantifying perfusion defects with Tc-99m sestamibi SPECT are also reported.

Johnson and Seldin discuss the clinical experience to date with Tc-99m teboroxime in the assessment of patients with chronic coronary artery disease. Their report describes a variety of imaging protocols and the results of a multicenter trial comparing Tc-99m teboroxime to Tl-201, coronary angiography, or both. The results suggest similar sensitivity and specificity of Tc-99m teboroxime to Tl-201, using either planar or SPECT approaches. These investigators provide interesting discussions of potential uses of the washout rate of Tc-99m teboroxime to quantitate regional myocardial blood flow, and of the potential advantages of multidetector SPECT with this agent. They also address the use of Tc-99m teboroxime for simultaneous assessment of exercise left ventricular ejection fraction and myocardial perfusion, based on preliminary work performed at Columbia University.

Jones, Borges-Neto and Potts describe the simultaneous measurement of myocardial perfusion and ventricular function during exercise using Tc-99m sestamibi. They report the results of rest-stress Tc-99m sestamibi studies using a multicrystal camera during treadmill exercise. Exercise ejection fraction is compared with the size of perfusion defects and quantitatively analyzed Tc-99m sestamibi SPECT studies. The investigators report a strong correlation between the indices of exercise ventricular function and myocardial perfusion, but also describe important differences in the information provided, suggesting a degree of independence between the measurements. They suggest that simultaneous assessment of exercise ventricular function and myocardial perfusion could improve the diagnostic and prognostic information of the radionuclide test. Their work may be the forerunner of a common clinical routine for the use of Tc-99m sestamibi to evaluate chronic coronary artery disease.

To conclude the fourth section, we compare SPECT and positron emission tomography (PET) approaches for

assessment of myocardial perfusion and viability. The state of the art Tl-201 SPECT is summarized as showing high sensitivity, a high normalcy rate and high reproducibility for assessment of myocardial perfusion. Tl-201 SPECT may have an advantage over the Tc-99m agents for assessment of myocardial viability, but SPECT with Tl-201 is limited by its suboptimal physical characteristics. Tc-99m sestamibi is ideally suited for standard and gated SPECT imaging. Tc-99m teboroxime SPECT is somewhat problematic due to the rapidly changing distribution of the tracer within the heart. PET is similar to Tl-201 with respect to assessment of myocardial perfusion, with perhaps slightly higher specificity. Tc-99m sestamibi SPECT, however, due to its higher energy, may have specificity very similar to that of PET perfusion studies. PET remains the "gold standard" for assessment of myocardial viability, but it has not yet been directly compared extensively to TI-201 reinjection protocols. The principal limitations of PET are the high costs of equipment and radiopharmaceuticals. It is suggested that the Tc-99m tracers will have a major impact on the clinical assessment of myocardial perfusion and viability.

The fifth section addresses special applications of Tc-99m sestamibi in chronic coronary artery disease, and the extensive European experience with this tracer. Taillefer provides a thorough description of his extensive studies using rest-stress same-day protocols for Tc-99m sestamibi imaging, and of the use of dipyridamole as an adjunct to Tc-99m sestamibi studies. While acknowledging that separate-day rest-stress protocols are ideal, this article addresses the advantages of the rest-stress over the stress-rest sequence when same-day protocols are used. It also provides promising preliminary results with respect to dipyridamole Tc-99m sestamibi studies.

Braat and associates discuss the special applications of Tc-99m sestamibi for determining the size of the myocardial area perfused by a coronary artery. The results of 2 separate protocols are provided. In 1 protocol, Tc-99m sestamibi is injected intravenously during the balloon occlusion phase of percutaneous transluminal coronary angioplasty. In the second, Tc-99m sestamibi is injected selectively into a coronary artery at the time of angiography. Later imaging then documents the area supplied by the coronary artery. The investigators suggest that the latter technique could be used to predict the area of jeopardized myocardium in the supply of a given coronary artery, since the uptake of the tracer is dependent on both myocardial perfusion and the presence of viable myocardium.

Sochor provides an overview of the European experience in which the results of multiple trials assessing Tc-99m sestamibi, both with planar and SPECT imaging, in

chronic coronary artery disease are summarized. Sochor also describes the results of a stress-rest sequence for Tc-99m sestamibi same-day studies (as compared with the rest-stress studies advocated by Taillefer). He reports a variety of studies that have addressed the assessment of ventricular function using either planar or tomographic techniques with Tc-99m sestamibi, as well as dual-isotope studies using Tc-99m sestamibi and indium-111 antimyosin for the simultaneous demarcation of zones of necrosis and zones of hypoperfusion.

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Experimental Studies of the Physiologic Properties of Technetium-99m Isonitriles

George A. Beller, MD, and Albert J. Sinusas, MD

Recently, efforts have been directed at the development of technetium-99m (Tc-99m)-labeled isonitrile compounds for assessment of regional perfusion and viability after experimental myocardial infarction or ischemia. One of the most promising of these agents, Tc-99m sestamibi, has undergone rather extensive laboratory investigation. Like thallium-201 (TI-201), the uptake of Tc-99m sestamibi in myocardial tissue is proportional to myocardial blood flow after intravenous injection. Similar to other diffusible indicators, Tc-99m sestamibi underestimates blood flow at high flow rates. In low flow regions, the myocardial uptake of this agent is higher relative to nonischemic uptake than is microsphere-determined blood flow. This is attributed to increased extraction at low flows. This first-pass myocardial extraction fraction for Tc-99m sestamibi is less than that for TI-201. However, Tc-99m sestamibi has a higher parenchymal cell permeability and higher volume of distribution than TI-201. Tc-99m sestamibi shows minimal "delayed redistribution" after initial intravenous administration.

Uptake of Tc-99m sestamibi is not altered by myocardial "stunning" or with ischemic dysfunction produced by sustained low coronary flow. The uptake of the isonitrile is still proportional to blood flow in these situations.

In intact animal models, myocardial uptake of Tc-99m sestamibi during coronary occlusion delineates the in vivo area at risk. When Tc-99m sestamibi is administered after reperfusion following variable periods of preceding coronary occlusion, Tc-99m sestamibi uptake delineates the area of viable myocardium that is salvaged and not simply the degree of reflow. This suggests that serial Tc-99m sestamibi imaging might be useful in assessing the efficacy of coronary reperfusion after thrombolytic therapy.

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nrecent years, new technetium-99m (Tc-99m)-labeled myocardial perfusion agents have been under laboratory and clinical investigation to determine their efficacy in evaluating regional myocardial blood flow and viability. More recently, efforts have been directed at the development of Tc-99m-labeled isonitrile compounds for the assessment of regional perfusion and viability after experimental myocardial infarction or ischemia either during sustained coronary occlusion or after reperfusion. One of the most promising of these agents is Tc-99mhexakis-2-methoxy-2-methylpropyl isonitrile (Tc-99m sestamibi), which is a lipophilic cationic Tc-99m complex that has the most favorable myocardial-to-background ratio for myocardial imaging of any of the isonitriles. The uptake and clearance kinetics of this new myocardial agent have been investigated in a number of experimental animal models.

INITIAL MYOCARDIAL DISTRIBUTION OF TECHNETIUM-99m SESTAMIBI

Myocardial uptake of Tc-99m sestamibi occurs in proportion to myocardial blood flow. 1-6 This property is similar to that of thallium-201 (Tl-201). Okada et al1 demonstrated a good correlation (r = 0.92) between microsphere-determined myocardial blood flow and Tc-99m sestamibi distribution using anesthetized dogs undergoing partial left circumflex coronary artery occlusion (Fig. 1). In a similar animal model, Glover and Okada⁶ demonstrated a linear relation (r = 0.97) between the initial myocardial uptake of Tc-99m sestamibi and regional myocardial blood flow at rates up to 2.0 ml/min/g when the agent was administered after an intravenous infusion of dipyridamole (Fig. 2). However, like other diffusible indicators, Tc-99m sestamibi was shown to underestimate myocardial blood flow at high flow rates (>2.0 ml/min/g). Li and coworkers³ showed that the myocardial distribution of Tc-99m sestamibi, as quantified from short-axis tomograms using a computerized circumferential profiles program, corresponded to regional myocardial perfusion by radioactive microspheres. After coronary reperfusion, Tc-99m sestamibi uptake in the center of the previously ischemic zone correlated well with recovery of flow as measured by the radioactive microsphere technique. The tomographic images showed resolution of the perfusion defect in all animals in which reperfusion was successful.

In low flow regions, the myocardial uptake of Tc-99m sestamibi is higher relative to nonischemic uptake than is the microsphere-determined regional blood flow. ^{2,3,5} This is attributed to the increased extraction of this agent at low flows comparable to what has been observed with

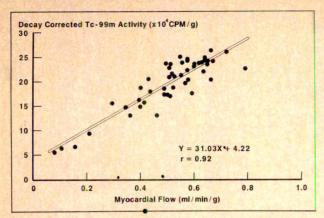


FIGURE 1. Relation of initial (microsphere) myocardial blood flow to technetium-99m (Tc-99m) sestamibi distribution. There is a linear relation with an r value of 0.92 (reproduced by permission of the American Heart Association¹).

radionuclide monovalent cations such as Tl-201. Canby et al² showed a close positive linear correlation between Tc-99m activity and microsphere-determined blood flow when Tc-99m sestamibi was given before reflow at the end of a 2-hour coronary occlusion interval. According to their data, there would be an excess of Tc-99m sestamibi above the level predicted on the basis of blood flow in zones where flow was reduced by approximately 10 to 40% of control flow. This observation was interpreted as increased extraction by viable myocardium during the 40-minute interval and not construed as being consistent with delayed redistribution. However, when flow decreased to between 0 and 10% of control, this increased extraction relative to flow was not evident. This was interpreted as being consistent with the reduced ability of infarcted nonviable myocardium to extract the tracer. Thus, these animals studies suggest that myocardial uptake of Tc-99m sestamibi is proportional to regional flow in the physiologic flow range with enhanced extraction of the tracer in low flow regions where myocardium is still viable.

As expected, there is an inverse relation between coronary blood flow and the fractional extraction of Tc-99m sestamibi. The first-pass myocardial extraction fraction for Tc-99m sestamibi is less than that for Tl-201. Studies by Leppo and Meerdink⁷ in the blood-perfused isolated rabbit heart showed that the mean peak value during the early plateau phase of extraction (E_{max}) for Tc-99m sestamibi (0.39) was significantly less than the mean E_{max} for Tl-201 (0.73) (Fig. 3). The net myocardial extraction (E_{net}), an estimate of myocardial retention, averaged 0.41 for Tc-99m sestamibi and 0.57 for Tl-201. Tl-201 was shown to have a higher transcapillary exchange rate than Tc-99m sestamibi. The mean capillary permeability-surface area product for Tc-99m sestamibi was approximately 33% of the value for Tl-201 (0.44 vs 1.30, respectively), but Tc-99m sestamibi had a significantly higher parenchymal cell permeability and higher volume of distribution than Tl-201. The overall effect of these differences in kinetics between Tc-99m sestamibi and Tl-201 is that little difference would be observed in the myocardial

uptake of the 2 agents when imaged in vivo. This is because capillary permeability for Tl-201 is higher than Tc-99m sestamibi but the reverse is true at the parenchymal cell wall.

In another study by Meerdink and Leppo⁸ using the same blood-perfused isolated rabbit heart model, hypoxia and ouabain had minor effects on peak myocardial extraction and the permeability-surface area product of Tc-99m sestamibi. Maublant et al9 showed, in myocardial cells in culture, that cyanide and iodoacetate (which profoundly affect myocardial metabolism by inhibiting the respiratory chain and glycolysis, respectively), did not affect Tc-99m sestamibi uptake and efflux, even in the presence of impaired contractile function. However, Tl-201 uptake was inhibited by the combination of cyanide and iodoacetate. Ouabain inhibition of sodium, potassium, adenosine triphosphatase also had no effect on Tc-99m sestamibi, but did affect Tl-201. Thus, it appears from these in vitro and in vivo experimental preparations that the uptake mechanisms of Tc-99m sestamibi are less dependent on active transport processes than are those of Tl-201. Intracellular extraction of Tc-99m sestamibi can proceed even with rather profound metabolic perturbations as long as the cell membrane is intact and cellular viability exists.

MYOCARDIAL CLEARANCE OF TECHNETIUM-99m SESTAMIBI

Tc-99m sestamibi shows negligible "delayed redistribution" after initial intravenous administration. Okada et al¹ assessed clearance of Tc-99m sestamibi in dogs subjected to circumflex coronary artery stenoses. Myocardial Tc-99m sestamibi activity in ischemic and nonischemic zones was continuously monitored with miniature implantable radiation detectors for 4 hours after injection of the radionuclide. In this model of severe low flow ischemia, the fractional Tc-99m sestamibi clearance over 4 hours was minimal in the ischemic (15 \pm 7%) and nonischemic (15 \pm 5%) zones. These data suggest that there

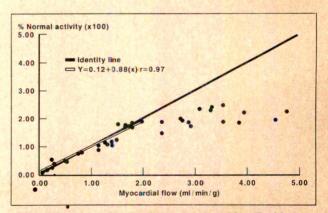


FIGURE 2. Scatterplet showing technetium-99m (Tc-99m) sestamibi activity (percent of normal zone activity) distribution versus microsphere-determined myocardial blood flow after dipyridamole. Tc-99m sestamibi distribution is linearly related to flow, up to approximately 2.0 ml/min/g. At higher flow rates, Tc-99m sestamibi distribution underestimates flow (reproduced by permission of the American Heart Association⁶).

is no appreciable redistribution of Tc-99m sestamibi, which is in contrast to the significant delayed redistribution seen with Tl-201 in similar canine experimental models. This important difference can probably be explained by at least 2 characteristics of Tc-99m sestamibi: (1) low blood levels of Tc-99m sestamibi, and (2) long myocardial retention. The result of both is that little Tc-99m sestamibi is available for reaccumulation.

EFFECT OF ISCHEMIA AND POSTISCHEMIC DYSFUNCTION ON TECHNETIUM-99m SESTAMIBI UPTAKE

We have shown that administration of Tc-99m sestamibi during reperfusion preceded by 15 minutes of transient coronary occlusion resulted in normal uptake of the radionuclide in the region of myocardial "stunning." Uptake of Tc-99m sestamibi in this model of stunned myocardium was comparable to uptake of Tl-201 and proportional to regional blood flow (Fig. 4).

Our group also assessed the myocardial uptake of Tc-99m sestamibi and Tl-201 under conditions of a chronic low flow state in an anesthetized open-chest canine model producing ischemic dysfunction. As shown in Figure 5, central ischemic Tc-99m sestamibi activity and Tl-201 activity (expressed as a percentage of the activity in the corresponding nonischemic zone) were comparable in endocardial and epicardial segments and proportional to flow at the time of tracer injection. These endocardial segments showed a good linear correlation between flow and activity of both Tl-201 (r = 0.78) and Tc-99m sestamibi (r = 0.85).

It can be concluded from these studies that ischemia, which produces profound systolic dysfunction, does not affect Tc-99m sestamibi or Tl-201 uptake as long as myocardial cells are still viable. Despite significant ischemia or postischemic systolic dysfunction in these models, the uptake of these radionuclides was still proportional to flow at the time of their administration. There was no flow-independent abnormality in myocardial uptake in

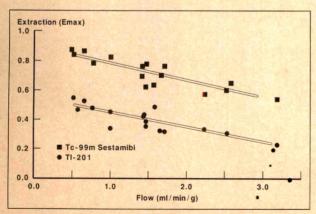


FIGURE 3. Comparison of technetium-99m (Tc-99m) sestamibi and thallium-201 (Tl-201) extraction (E_{max}) values versus coronary blood flow. Linear least-squares regression *lines* are shown; the *top line* represents Tc-99m sestamibi, and the *bottom line* represents Tl-201 (reproduced by permission of the American Heart Association⁷).

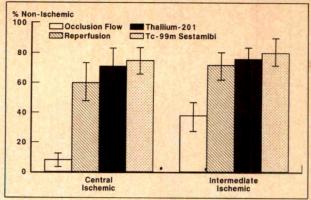


FIGURE 4. Regional blood flow and myocardial activity. Illustrated are occlusion and reperfusion flow and thallium-201 and technetium-99m (Tc-99m) sestamibi activity for central ischemic (n = 29) and intermediate ischemic (n = 21) endocardial segments expressed as a percent of nonischemic segmental flow. Both thallium-201 and Tc-99m sestamibi activity levels were comparable with reperfusion flow in central and intermediate ischemic segments (reproduced by permission of the American College of Cardiology⁵).

the ischemic or "stunned" myocardial tissue. This lends support to the concept that Tc-99m sestamibi can be extracted intracellularly as long as cell membrane integrity is intact.

QUANTIFICATION OF RISK AREA DURING CORONARY OCCLUSION AND MYOCARDIAL SALVAGE AFTER REPERFUSION USING TECHNETIUM-99m SESTAMIBI

Several studies have been performed to assess whether myocardial imaging with Tc-99m sestamibi is useful for assessing risk area during coronary occlusion and extent of salvaged myocardium after coronary occlusion followed by reperfusion. Verani and coworkers⁴ found that the scintigraphic perfusion defect size correlated well with pathologic infarct size (r = 0.85 and r = 0.95 by planar and tomographic imaging, respectively) during 2

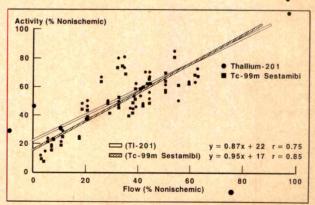


FIGURE 5. Central ischemic endocardial activity versus flow. Illustrated is the correlation of thallium-201 (TI-201) and technetium-99m (Tc-99m) sestamibi activity and stenotic flow among those endocardial segments in which stenotic flow was reduced to $\leq\!60\%$ of preocclusion flow (reproduced by permission of the American College of Cardiology⁵).

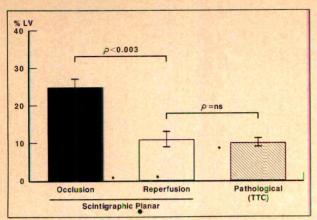


FIGURE 6. Comparison of planar scintigraphic perfusion defect size during occlusion and reperfusion with pathologic infarct size in 12 dogs. LV = left ventricle; TTC, = triphenyltetrazolium chloride (reproduced by permission of the American College of Cardiology⁴).

hours of coronary occlusion in a canine model. The planar defect size, but not the tomographic defect size, overestimated the pathologic size. After 48 hours of reperfusion, scintigraphic defect size was markedly reduced. Uptake of Tc-99m sestamibi in ischemic myocardium increased significantly and correlated with the increase in regional flow as assessed by microspheres. Figure 6 compares the planar scintigraphic defect size during occlusion and reperfusion with the pathologic infarct size in 12 dogs in this study.

More recently, we have defined in our laboratory the myocardial distribution of Tc-99m sestamibi before and after coronary reperfusion in open-chest anesthetized dogs that underwent 3 hours of left anterior descending occlusion followed by 3 hours of reflow. 10 When intravenous Tc-99m sestamibi was administered during occlusion only, the risk area defined by autoradiography correlated (r = 0.94) with the postmortem risk area, although it was somewhat smaller. This was thought to be due to the presence of collateral flow in vivo, which would not influence the postmortem risk area. In dogs receiving Tc-99m sestamibi 90 minutes after coronary reperfusion that was preceded by 3 hours of occlusion, Tc-99m sestamibi activity was less than reperfusion flow. The defect area defined by Tc-99m sestamibi autoradiography correlated closely with the postmortem infarct size (r = 0.98) in these reperfused dogs, as assessed by the dual simultaneous perfusion of monastral blue into the left main coronary artery and triphenyltetrazolium chloride into the left anterior descending artery distal to the occlusion under physiologic pressures.

Thus, the results of these animal studies indicate that the myocardial uptake of Tc-99m sestamibi during coronary occlusion correlates with occlusion flow and delineates the in vivo "area at risk." When Tc-99m sestamibi is given after reperfusion following variable periods of preceding coronary occlusion, Tc-99m sestamibi activity uptake delineates the area of viable myocardium that is salvaged, with defect size correlating well with pathologic infarct size. These data are consistent with clinical imaging studies that have shown that serial Tc-99m sestamibi imaging is useful in assessing the efficacy of coronary reperfusion in patients receiving thrombolytic therapy. 11,12 The experimental studies suggest that in the presence of acute infarction, Tc-99m sestamibi uptake during reperfusion reflects both the degree of reflow and the extent of viable myocardium. Hence, its properties are not simply akin to inert microspheres that merely measure regional myocardial blood flow after reperfusion.

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Experimental Studies of the Physiologic Properties of Technetium-99m Agents: Myocardial Transport of Perfusion Imaging Agents

Denis J. Meerdink, PhD, and Jeffrey A. Leppo, MD

The physiologic properties of new technetium-99m-labeled myocardial imaging agents (Tc-99m sestamibi, an isonitrile; and Tc-99m teboroxime, a boronic acid adduct of technetium dioxime) are discussed and compared to thallium-201 (TI-201). Studies with isolated hearts, subcellular fractions and cell cultures indicate that Tc-99m sestamibi, Tc-99m teboroxime and Tl-201 do not share common transport or sequestration mechanisms. Although peak Tc-99m sestamibi myocardial extraction over time is about half that of TI-201 at equivalent coronary blood flows, the amount of Tc-99m sestamibi that remains in the heart is similar to that of TI-201 because of its higher retention efficiency. The high retention efficiency for Tc-99m sestamibi also results in minimal redistribution. In contrast, Tc-99m teboroxime myocardial extraction is higher than that of TI-201, but its retention is less efficient, resulting in relatively rapid washout characteristics which may quickly result in tracer redistribution. During reperfusion after a noflow period, Tc-99m sestamibi extraction and retention increase, but for Tc-99m teboroxime and TI-201 these values tend to decrease. All tracers show adequate transport characteristics for perfusion imaging, and differences in transport and retention should lead to the development of new clinical protocols.

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The study of cardiac dysfunction has benefited from the development of standard nuclear cardiology techniques over the past 10 to 15 years, and valuable medical insight into coronary perfusion has been gained from the use of single photon tracers. Although thallium-201 (Tl-201) is the most widely used clinical myocardial perfusion agent, technetium-99m (Tc-99m)labeled perfusion agents offer several advantages. Since Tc-99m is available from a generator in a nuclear medicine laboratory 24 hours/day, special deliveries from a commercial radiopharmacy or distribution center are not required. The energy of Tc-99m (140 keV) is ideal for standard gamma camera imaging, which can result in an improved resolution on a count-by-count basis due to less scatter and attenuation in the patient and stronger scintillations with the detector crystal. Finally, the improved radiation dosimetry and much shorter half-life of Tc-99m compared to Tl-201 permits the injection of 10 times as much radioactivity. Consequently, it is likely that the use of Tc-99m-labeled agents will significantly increase and expand the nuclear cardiology field.

Recently, Tc-99m-labeled compounds, such as the isonitriles and boronic acid adducts of technetium dioxime (BATO) compounds, have shown promise as myocardial perfusion agents. [Tc-99m]-hexakis(2-methoxyisobutylisonitrile) is an isonitrile generically known as Tc-99m sestamibi, and also called MIBI, RP30 or Cardiolite™ (E.I. du Pont de Nemours & Co.).1,2 The BATO compounds (complexes) are stable, neutral and lipid soluble.3,4 [Bis[1,2-cyclohexanedione dioximato (1-)-O]-[1,2-cyclohexane-dione-ioximato(2-)-O] methyl-borato(2-)-N,N',N",N",N"",N""]-chlorotechnetium, is a BATO compound that is also referred to as Tc-99m teboroxime, SQ30217 or Cardiotec™ (Squibb Diagnostics). Thorough knowledge of cellular tracer uptake, distribution and retention and of the physiologic factors that affect capillary-tissue exchange and tissue retention are important for accurate interpretation of perfusion images. This information can only be determined using several independent methodologic approaches. The goal of this review is to summarize the physiologic properties of new technetium isonitrile and BATO agents and compare them to those of Tl-201.

ISOTOPE TRANSPORT ANALYSIS

Indicator dilution: A powerful and useful technique to study perfusion tracers is indicator-dilution analysis. A tracer bolus is injected into the arterial inflow, and dilu-

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TABLE I Capillary-Tissue Exchange Equations (1) Transport function: h(t) $h(t) = F = C(t)/q_0$ where F = plasma flow (ml/min) t = time after injection (min or s) C(t) = isotope activity (cpm/g) q₀ = injected dose (cpm) (2) Maximum tissue extraction: E(t) $E(t) = 1 - h_D(t)/h_R(t)$ where $h_D(t) = diffusible h(t)$ (e.g., TI-201, Tc-99m sestamibi or Tc-99m teboroxime) $h_R(t) = albumin reference h(t)$ (3) Capillary permeability-surface area product: PScap $PS_{cap} = -F_s \cdot log_e (1 - E_{max})$ where $F_s = plasma or solute flow (ml/min/g)$ E_{max} = maximum diffusible E(t) up to peak $h_R(t)$ (4) Net tissue extraction: Ener(t) $E_{\text{net}}(t) = \int_{0}^{t} [h_{R}(t) - h_{D}(t)] d\lambda \div \int_{0}^{t} h_{R}(t) d\lambda$ where λ is a dummy variable for integration Overall E_{net} is at t (s) when 99.99% of albumin has emerged. Tc-99m = technetium 99m; Tl-201 = thallium-201.

tion patterns are analyzed in the venous outflow. Tissue extraction, retention and capillary permeability are calculated from dilution curves of diffusible tracers (Tl-201, Tc-99m sestamibi or Tc-99m teboroxime) and a concurrently injected impermeable tracer (labeled albumin). Transcapillary transport and myocardial retention of the permeable tracers are affected not only by perfusion rate and capillary permeability, but also by the binding characteristics in the tissue. Retention of tracer by the myocardial tissue is affected by altered intracellular binding or, conceivably, by changes in binding to interstitial structures.

Isolated perfused heart: The isolated perfused heart is particularly useful for characterizing tracer kinetics because physiologic parameters can be controlled independently (e.g., flow, work, substrate availability, drug delivery and recirculation). In the Langendorff preparation, the heart is perfused retrogradely through the aorta, either under constant pressure or constant flow. 5,6 The heart preparation can be paced and is more "physiologic" when perfused with either whole blood or washed erythrocytes to maintain tissue oxygen delivery at "normal" flow rates. In addition, the isolated perfused heart has been used to study the effect of different physiologic and pharmacologic interventions.

Tracer selection: Although the rapid emergence of Tc-99m-labeled perfusion agents has resulted in widespread clinical studies, additional basic investigations are needed to adequately evaluate the myocardial transport properties of these agents. It is important to critically define the effects of flow and metabolic alterations on isotope transport in the heart. Since these cardiac isotopes are diffusion-limited substances, myocardial capillarytissue exchange has been successfully evaluated by analyzing the dilution in venous outflow of multiple indicators injected simultaneously into the arterial inflow. A multiple-indicator cocktail is used consisting of a mixture of diffusible tracers, radiolabeled albumin (vascular reference) and ethylenediaminetetraacetic acid (EDTA, an interstitial space marker). The combination of isotopes used in the cocktail is limited by the individual energies of the isotopes and the ability of the counting equipment to reliably distinguish individual isotopes.

Data analysis: After the cocktail is injected as a bolus into the arterial inflow, venous effluent is collected at constant time intervals determined by the perfusion rate. The total time of collection, typically 2 to 4 minutes, is established to ensure collection of all injected reference tracer (albumin) so that reliable estimates of the retention of diffusible tracer can be calculated.

Numerical analysis of the venous outflow samples uses the equations in Table I. For each sample, normalized transport function curves are calculated for each of the tracers [albumin (reference), h_R(t); Tl-201, Tc-99m sestamibi or Tc-99m teboroxime (diffusible), h_D(t)] using equation 1. The h(t) transport functions represent the fraction of injected tracer emerging from the heart/second and are used to calculate the other exchange estimates⁷⁻⁹ E_{max}: the maximum fractional tissue extraction, equation 2; PS_{cap}, the capillary permeability-surface area product (Crone), equation 3; and Enet, the overall net tissue extraction, equation 4. These variables, which represent estimates of capillary-tissue exchange and flux as well as the amount of tracer retained by the heart, are explained in the following sections.

A close examination of the plots of the exchange estimates versus time (Figs. 1 and 2) reveals important differences among the tracers. The h(t) curve represents a flow-proportional fraction of injected dose observed at each time point. The shape of the h(t) curve, which characteristically has a rapid rise to a relatively sharp peak followed by a gradually decreasing "tail" portion, results from several factors. Because albumin can be assumed to remain confined in the vasculature during the short duration of the indicator-dilution experiment, the albumin h(t) curve (Figs. 1A and 2A) demonstrates the dispersion resulting from heterogeneous flow in the cardiac vasculature as well as laminar flow in the system. However, the shapes of the h(t) curves for the diffusible tracers result from not only this dispersion from flow, but also from the escape of tracer from the vasculature into extravascular compartments (interstitium, membranes and parenchymal cells). Therefore, the difference between the h(t) of albumin and the h(t) of Tl-201, Tc-99m sestamibi or Tc-99m teboroxime indicates an escape of diffusible tracer from the perfusate as it passed through the heart. This is the instantaneous fractional extraction, E(t), which is plotted for Tc-99m sestamibi and Tl-201 in Figure 1B and for Tc-99m teboroxime and Tl-201 in Figure 2B. The Tl-201 and Tc-99m teboroxime overall E(t) patterns are typical for cations (rapid rise and rapid fall during the h(t) peaks), although Tc-99m teboroxime is a neutral lipophilic compound. The E(t) for Tc-99m sestamibi is relatively low during the h(t) peak, but continues a gradual increase during the entire experimental period. The permeability-surface area product or tracer flux at the capillary/interstitial compartmental interface (PS_{cap}) is derived from the flow rate of the solute (F_S) and

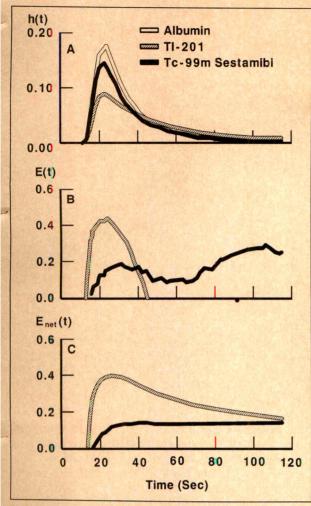


FIGURE 1. A, representative transport functions [h(t), albumin open line], B, instantaneous fractional extraction [E(t)] and C, net extraction $[E_{net}(t)]$ for technetium-99m (Tc-99m) sestamibi and thallium-201 (TI-201).

the E_{max} value. The E_{max} value is not necessarily the highest E(t) value observed over the entire experimental period, but is the highest E(t) observed up to and including the albumin peak. This limitation is needed because the PS_{cap} calculation assumes unidirectional tracer flux.

E_{net} is an estimate of net tissue exchange with time, or if an appropriate end point is defined, the retention of diffusible tracer by the tissue over the specified time course. Comparison of the h(t) curves with their respective E_{net}(t) plots (Figs. 1C and 2C) reveals important differences in the myocardial exchange and retention of the diffusible tracers. The numerator of the E_{net} equation is the area of the albumin transport curve [h(t)] minus the diffusible tracer's h(t) area; the denominator of the equation [albumin h(t) area] normalizes the calculation. The numerator is positive (indicating a net blood-to-tissue transport) when the albumin curve is above the diffusible h(t) curve (Tl-201, Figs. 1C and 2C; Tc-99m sestamibi, Fig. 1C; Tc-99m teboroxime, Fig. 2C), and the slope of the E_{net}(t) curve is positive. When the albumin h(t) curve is lower than the diffusible h(t) curve, such as during the tail portion for Tl-201 (Figs. 1C and 2C) or for Tc-99m teboroxime (Fig. 2C), the numerator is negative

[thus a negative $E_{net}(t)$ slope], which indicates a net clearance of tracer from the extravascular to intravascular space. Thus, despite its much lower peak extraction (E_{max}) , Tc-99m sestamibi h(t) remains below the albumin reference throughout the observation period, and a persistent net blood-to-tissue exchange is demonstrated. Consequently, the $E_{net}(t)$ curve for Tc-99m sestamibi maintains a positive slope. In contrast, Tl-201 and Tc-99m teboroxime have a net blood-to-tissue exchange only during the early portion of the h(t) curve, but a net tissue-to-blood exchange during the tail portion. In addition, the Tc-99m teboroxime E_{net} function decreases more quickly than that for Tl-201, suggesting a faster back diffusion of initially extracted tracer.

COMPARISON OF TECHNETIUM-99m SESTAMIBI AND THALLIUM-201

The myocardial transport of TI-201 and Tc-99m sestamibi have been compared during variable blood flow

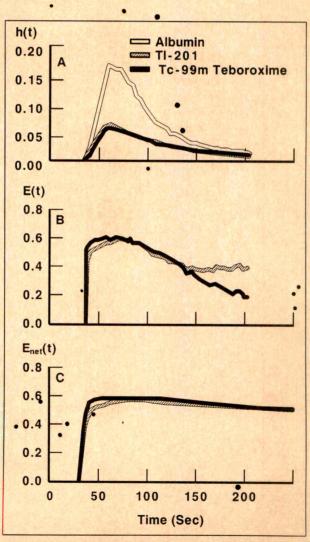


FIGURE 2. A, representative transport functions [h(t)], albumin open line), B, instantaneous fractional extraction [E(t)] and C, net extraction $[E_{net}(t)]$ for Tc-99m teboroxime and Tl-201. Abbreviations as in Figure 1.

TABLE II Exchange Estimates for Tc-99m Sestamibi and

	Tc-99m Sestamibi		TI-201	
	Mean	S.D.	Mean	S.D.
E _{max} PS _{cap} (ml/min/g)	0.39 0.44	0.09 0.12	0.73 1.30	0.10 0.45
E _{net}	0.41	0.16	0.57	0.13

 $E_{\rm net}$ values were calculated over 1.5 to 4 minutes after injection. Blood flow = 1.51 (±0.76) ml/min/g; $E_{\rm max}$ = maximum tissue extraction; $E_{\rm net}$ = net tissue extraction; SD = standard deviation; other abbreviations as in Table I.

levels in 9 blood-perfused, isolated rabbit hearts. ¹⁰ Using indicator-dilution techniques, 17 injections of a mixture containing radiolabeled albumin, radiolabeled EDTA, Tl-201 and Tc-99m sestamibi were administered. The transport data from these experiments are listed in Table II. The mean E_{max}, PS_{cap} and E_{net} values for Tc-99m sestamibi were all significantly less than the corresponding Tl-201 determinations (p <0.001). However, computer modeling estimates of parenchymal cell distribution and permeation for Tc-99m sestamibi were significantly greater than corresponding Tl-201 measurements. This accounts for the relatively high cellular retention of Tc-99m sestamibi and relatively small disparity in E_{net} values compared to E_{max} and PS_{cap}.

Figure 3 shows the individual (n = 16) values of $E_{\rm max}$ and coronary blood flow for both Tl-201 and Tc-99m sestamibi. There is a negatively sloped linear relation between $E_{\rm max}$ and blood flow for each tracer, and Tc-99m sestamibi values are always less than corresponding Tl-201 determinations. The least squares best fit linear regression line for $E_{\rm max}$ is also shown for both isotopes: Tc-99m sestamibi = $0.51-0.09 \times$ flow (r = -0.80) and Tl-201 = $0.91-0.11 \times$ flow (r = -0.85).

These data suggest that capillary permeability for Tl-201 is greater than for Tc-99m sestamibi, with the reverse true at the parenchymal cell membrane. The mechanism of cellular transport is different for these 2 tracers, and both have adequate characteristics to permit myocardial perfusion imaging. Marshall et al¹¹ reached a similar conclusion using a comparable protocol. These investigators reported mean peak extraction values of 0.57 for Tc-99m sestamibi and 0.80 for Tl-201, and 2.5-fold greater myocardial retention for the Tc-99m compound.

Okada et al¹² noted no changes in fractional Tc-99m sestamibi clearance rates from either normal or ischemic cardiac zones of open-chest dogs with coronary artery disease. Using miniature, implanted radiation-detecting probes, the mean 4-hour fractional clearances measured for Tc-99m sestamibi averaged 0.15, representing a fairly minimal washout rate. Over the same period, mean Tc-99m sestamibi blood clearance was 0.98. These data agree nicely with the in vitro rabbit heart observations and suggest that Tc-99m sestamibi has very stable tracer distribution and is thus well suited for single photon emission computed tomography (SPECT) imaging.

In experiments by Meerdink et al¹³ performed in isolated rabbit hearts, transport of Tc-99m sestamibi and Tl-201 were evaluated at control and after 5 and 30

minutes of reperfusion (after 30 to 60 minutes of 0-flow ischemia). Tl-201 peak extraction showed a small but significant decrease during reperfusion in both groups of hearts. Mean E_{max} values reported were 0.62 at control, 0.60 at 5 minutes of reperfusion and 0.56 at 30 minutes of reperfusion. Tc-99m sestamibi peak extraction increased from a control value of 0.22 to 0.23 and 0.31 at 5 minutes and 30 minutes of reperfusion, respectively. It should be noted that Tl-201 peak extraction values were always greater than simultaneously determined Tc-99m sestamibi values.

Tl-201 E_{net} or net extraction of injected tracer dose showed a significant decrease during reperfusion, from a mean E_{net} of 0.35 to 0.32 at 5 minutes of reflow and 0.17 at 30 minutes of reflow. In contrast, Tc-99m sestamibi E_{net} progressively increased with reperfusion. The mean E_{net} was 0.20 at control, 0.26 at 5 minutes of reflow and 0.34 at 30 minutes of reflow. Tl-201 values were noted to be greater than simultaneously determined Tc-99m sestamibi values only at control and 5 minutes of reperfusion, but were clearly lower after 30 minutes of reflow.

There is a slight decrease in the myocardial transport of Tl-201 in the first hour of coronary reperfusion. In contrast, Tc-99m sestamibi transport is enhanced. The mechanisms of the changes in exchange and retention are not known. However, because Tc-99m sestamibi transport into myocardial tissue is limited primarily by its capillary exchange, changes in capillary permeability after ischemia/reperfusion are a likely mechanism of enhanced Tc-99m sestamibi transport. This also suggests that cellular or metabolic function can primarily affect myocardial tracer uptake of Tl-201 and Tc-99m sestamibi during acute coronary reperfusion.

Liu et al¹⁴ have also noted enhanced Tc-99m sestamibi transport during coronary reperfusion in a bufferperfused rat heart having constant isotope infusion. However, Sinusas et al¹⁵ observed a diminished Tc-99m sestamibi uptake in open-chest dogs after 90 minutes of reperfusion preceded by 3 hours of coronary occlusion. Therefore, the duration of prior coronary occlusion and the timing of Tc-99m sestamibi administration after reflow may have a critical effect on its transport.

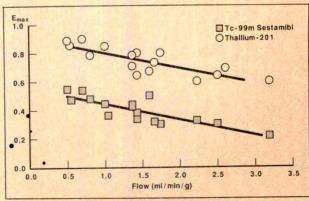


FIGURE 3. Maximum fractional extraction (E_{max}) versus flow (ml/min/g) for Tc-99m sestamibi and Tl-201 (reproduced with permission of the American Heart Association 10). Abbreviations as in Figure 1.

COMPARISON OF TECHNETIUM-99m TEBOROXIME AND THALLIUM-201

An isolated blood-perfused rabbit heart model was used with multiple-indicator dilution techniques to compare the myocardial transport of 2 Tc-99m-labeled BATO compounds (Tc-99m teboroxime and Tc-99m SQ32014) and Tl-201 during variable levels of coronary flow. 16 The experimental protocol involved an initial stabilization period for each heart before the injection of a multiple-indicator cocktail containing Tl-201, Tc-99m teboroxime and indium-111 albumin. The individual values for each Tc-99m teboroxime and Tl-201 Emax determination are shown in Figure 4. The least squares linear regression lines are also displayed. Although the slopes are similar, it is clear that each Tc-99m teboroxime Emax is higher than the simultaneously determined Tl-201 value. Tl-201 and Tc-99m teboroxime show an inverse linear relation between E_{max} and coronary blood flow.

The individual values for each Tc-99m teboroxime and Tl-201 PScap determination are shown in Figure 5. The capillary flux for Tc-99m teboroxime is always higher than simultaneously determined Tl-201 values, but both tracers show a plateau effect at coronary flows >1.5 ml/min/g. This probably represents diffusion limitation at the capillary level. There is a direct linear relation between PScap and flow for Tc-99m teboroxime and Tl-201. Coronary flow averaged 1.31 ml/min/g and varied from 0.30 to 2.44 ml/min/g. Mean Tc-99m teboroxime extraction was 0.71 and was 25% higher than the mean TI-201 E_{max} of 0.57 (p <0.001). The mean PS_{cap} for Tc-99m teboroxime was 1.1 ml/min/g, and this was also higher (46%) than the mean Tl-201 PScap of 0.75, (p <0.001). The mean E_{net} for Tc-99m teboroxime was 0.55 ± 0.19 , which was only 20% higher than the average Tl-201 values. Enet calculations account for both the initial transcapillary permeation as well as the back diffusion.

Although Tc-99m teboroxime has a higher net retention than Tl-201, this important parameter shows a relatively smaller disparity than might have been expected based on the observed differences in E_{max} and PS_{cap}. Other preliminary results by Stewart et al¹⁷ in open-chest

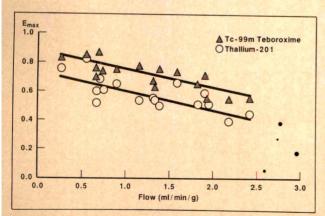


FIGURE 4. Maximum fractional extraction (E_{max}) versus flow (ml/min/g) for Tc-99m teboroxime and Tl-201 (reproduced with permission 16). Abbreviations as in Figure 1.

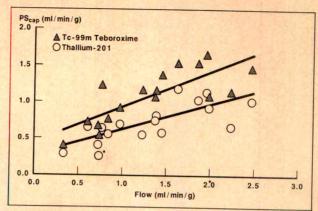


FIGURE 5. Permeability-surface area product (PS_{cap}) versus flow (ml/min/g) for Tc-99m teboroxime and Tl-201 (reproduced with permission 16). Abbreviations as in Figure 1.

dogs show relatively high extraction of Tc-99m teboroxime after intracoronary injections. In addition, Tc-99m teboroxime cellular clearance appears to be flow related and fairly rapid.

Clinical trials have shown that this agent can be used for perfusion imaging. ¹⁸ These basic experiments suggest that capillary flux of Tc-99m teboroxime is greater than that of Tl-201, but there appears to be smaller myocardial retention of the initially extracted BATO tracer. Clinical protocols should take advantage of these characteristics by rapidly collecting myocardial perfusion scans, completing initial imaging by 10 to 15 minutes after injection.

SUBCELLULAR LOCALIZATION

In normal muscle tissue, the kinetics of Tl-201 are similar to those of potassium. 19 The myocardial transport of Tl-201 is determined primarily by coronary perfusion. with hypoxia and contractile state being relatively unimportant. 6,20 In a study with cultured heart cells, 21 Tl-201 uptake was not affected by cyanide-induced hypoxia or by inhibition of glycolysis or sodium/potassium adenosine triphosphatase, but it did increase with pH; Tc-99m sestamibi uptake was unaffected by any experimental treatment. The investigators concluded that Tl-201 and Tc-99m sestamibi uptake occurred by different mechanisms and that Tc-99m sestamibi was less sensitive to metabolic changes than Tl-201. However, in studies with perfused guinea pig heart, Tc-99m sestamibi uptake was reduced by extreme hypoxia, while Tl-201 uptake was unaffected.22 In studies with isolated erythrocyte membranes, Tl-201 influx was depressed with ouabain. 23 It is likely that Tl-201 uptake uses a potassium-like mechanism (adenosine triphosphatase and others),24 while Tc-99m sestamibi uptake is related to its lipophilicity²² similar to its parent Tc-99m-t-butyl isonitrile compound.²³

The mechanisms for exchange and retention of Tc-99m teboroxime are not well established, but would be dominated by nonionic mechanisms since the BATO compounds are neutral, lipophilic compounds. Additional studies will be important to critically evaluate these issues.

Cells ²⁵				
	1 Minute (%)	10 Minutes (%)		
Tc-99m sestamibi	175	166		
TI-201 (norm)	100	100		
Tc-99m teboroxime	445	377		

	T _{1/2} (minutes)		
	• Uptake	Release	Ci/e*
Tc-99m sestamibi	35	28	155
TI-201	5	6	136
Tc-99m teboroxime	<2	13 •	585

TABLE V Myocardial Transport Summary 10,16					
Capillary permeation Tc-99m teboroxime >> TI-201 >> Tc-99m sestamibi					
Net retention (extraction)					

Early: Tc-99m teboroxime > Tl-201 > Tc-99m sestamibi Late: Tc-99m sestamibi > TI-201 > Tc-99m teboroxime Parenchymal cell permeation/distribution

Tc-99m sestamibi >>> Tl-201 >>> Tc-99m teboroxime

Abbreviations as in Table I.

CELL CULTURE DATA

Myocardial cells grown with special culture methods can be used to study tracer "uptake" in different experimental protocols. In general, different isotopes are incubated for variable times in identical cell culture lines and the medium is then removed. After measuring radiation activity in detached cells (normalized for protein content), a determination of cell-associated activity can be made or further normalized to the tracer activity remaining in the buffer media (intra- to extracellular ratio). The net clearance of tracer from these cells can also be evaluated by placing previously incubated cells into isotopefree medium. A washout curve can be calculated from the amount of activity remaining in the cells and released to the "cold" buffer over time.

Although these cardiac cells are functioning in culture, the movement of isotope in these experiments does not have a clear clinical application. There is no flow and no variation in tracer concentration, and there are no capillary-tissue barriers. Nonetheless, this is a well-established experimental technique and merits careful review.

Data reported by Kronauge et al²⁵ suggest that chick heart cells initially accumulate Tc-99m sestamibi faster than Tl-201 (all observations are normalized to Tl-201 uptake) and that Tc-99m teboroxime uptake is even faster (Table III). This work involves a technique previously reported for another isonitrile compound.26 The cellular

tracer activity remains fairly stable over 10 minutes with only a slight tendency for Tc-99m teboroxime activity to decrease. Overall, these data suggest greater cellular accumulation for the Tc-99m-labeled agents than for Tl-

In another cell culture line, Maublant et al21,27 have shown that Tc-99m teboroxime has the fastest uptake and greatest accumulation (Ci/e) of all 3 agents (Table IV). Tl-201 has relatively fast uptake and the quickest release, which results in the lowest net accumulation (after 3 hours). Tc-99m sestamibi has the slowest uptake and release of the 3 tracers, but shows a greater net accumulation than Tl-201.

Both types of cell culture techniques can be used to study the effect of varying levels of metabolic or cellular inhibitions. Extensive interventions have been reported involving inhibition of membrane transport, glycolysis and the respiratory chain (cytochrome oxidase). While variable results have been reported, in general it appears that Tc-99m teboroxime is the least and Tl-201 is the most sensitive to metabolic inhibition at the cellular level.

SUMMARY

Data from perfused heart studies are summarized in Table V. Transport at the capillary level is fastest for Tc-99m teboroxime and slowest for Tc-99m sestamibi. Because the initial transport rate of Tc-99m teboroxime is quite high and that of Tc-99m sestamibi is lower, Tc-99m teboroxime's net extraction is much higher than that of Tc-99m sestamibi during relatively early periods of time. However, at relatively later time periods (10 to 20 minutes), the extent of net extraction reverses because Tc-99m teboroxime retention is much less than that of Tc-99m sestamibi. Based on some modeling assumptions, transport at the interstitial-parenchymal cell barrier is highest for Tc-99m sestamibi, and Tc-99m teboroxime has the smallest amount of intracellular distribution, which contributes to the observed temporal changes in net extraction.

Overall, Tc-99m teboroxime, Tl-201 and Tc-99m sestamibi have very different cardiac transport mechanisms. Therefore, imaging protocols will need to be optimized for each particular type of study (both tracer and clinical situation). It now appears clear that nuclear cardiology will expand into new areas of coronary blood flow imaging with a full complement of perfusion agents.

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Technical Aspects of Myocardial Planar Imaging with Technetium-99m Sestamibi

William H. Smith, MS, and Denny D. Watson, PhD

Fundamental quantitative planar imaging techniques, evolved over the years, have been adapted to maximize the efficiency and clinical effectiveness of technetium-99m (Tc-99m) sestamibi imaging. To ensure reproducible image interpretation, the Society for Motion Picture and Television Engineers test pattern is used to obtain the necessary standardization of video and hard copy images. A standardized intensity scale intuitively relates count density to perceived brightness. Data are accumulated via standard 16-frame multiple gated acquisition and can be viewed in cine mode to assess wall motion. The images are then automatically summed for quantitative analysis of myocardial perfusion. Excessive extracardiac Tc-99m activity is automatically suppressed by the computer program to prevent suboptimal display of the heart. Due to the difference in heart background ratio and shape of the extracardiac background between resting and exercise Tc-99m sestamibi images, a modified interpolative background subtraction algorithm was developed. Image registration is necessary for accurate comparison of the rest and exercise images to detect redistribution. This is automatically accomplished by adjusting the position of the background-subtracted and centered images so as to maximize the cross-correlation coefficient. Profiles are generated to sample the myocardial count distribution and can be compared to a normal database, subject to confirmation by a competent interpreter. Rest redistribution is defined by a change in the myocardial distribution of Tc-99m sestamibi between exercise and rest images. Flashback display is used to identify subtle regions of redistribution that often signify residual viability within an infarct zone. In this technique, which maintains standard anatomic images for the interpreter, exercise and rest background-corrected images are brought into registration and each scaled to its maximum count so that alternate images can be flashed on the screen in the same position. Redistribution in a myocardial segment will appear as a sudden shift of intensity relative to the remainder of the image during flashback.

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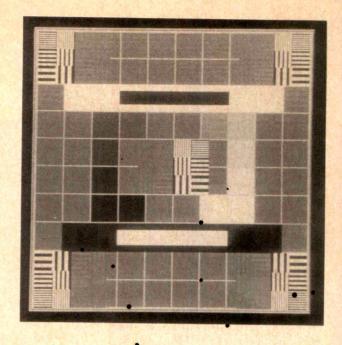
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Thy consider planar imaging when technetium-99m (Tc-99m) sestamibi is so ideally suited to single photon emission computed tomography (SPECT)? Planar imaging is still commonly performed and may reflect greater experience and refinement of technique. Gated planar imaging can be performed using available multiple gated acquisition (MUGA) software and hardware. This can add wall motion assessment to myocardial perfusion imaging using a well-developed familiar technique. It requires no additional imaging time because the gated image set can be summed to obtain a static image for quantitative image analysis. Methods discussed herein are available now for precise registration and subtraction of planar images, which will facilitate split dose or simultaneous dual isotope imaging. Planar imaging is better suited for studies at bedside or in a critical care situation and requires less radionuclide dose and less strenuous patient positioning. Spatial resolution will necessarily be slightly better in planar images, and there will be less distortion from partial volume effects. The intrinsic detectability of defects must be the same since SPECT images are constructed from planar input images and the computer cannot create valid defects if these defects are not present in the input planar image data. It should be emphasized that special methods of background subtraction and meticulous image control are required for comparable defect visualization in planar images because intrinsic defect contrast is greater with SPECT. While higher contrast is often assumed to result in higher sensitivity for defect detection, this assumption is not strictly correct. A defect can be "detected" only if the signal-to-noise ratio is statistically significant. Increasing contrast will not per se improve the statistical significance of signal to noise. SPECT cannot decrease the statistical noise contained in the input data that will propagate through the mathematical reconstruction. Consequently, while higher image contrast may lead to visual identification of more defects, which will always improve sensitivity, the result may be achieved at the expense of lower specificity.

SPECT images are computed from mathematically complex reconstruction algorithms so that it may not be clear, for example, how a simple motion or attenuation artifact in the planar input images will be reconstructed into the computed tomographic images. As a result of the 3-dimensional reconstruction, defect localization should be better in SPECT images, but this advantage may not always outweigh the cost of increased complexity. Finally, the fundamentals of good planar imaging that were learned over the years can serve as well for SPECT imaging. Examples of this are the standardization of images, the method of image registration to ensure identical sam-

FIGURE 1. The Society for Motion Picture and Television Engineers pattern is designed to test many details of the video display or hard copy reproduction. The inner ring of squares is a gray scale. To the right of the black square is another black square with an inset square at 5% intensity. To the left of the white square is a white square with a 95% inset. The low-contrast bar patterns are produced at 1, 3 and 5% modulation. These features will be visible only if the image reproduction is excellent. They may not be visible in this half-tone reproduction of the test pattern.



pling of rest and stress images, and the flashback technique for highlighting regions of ischemia. These techniques are all applicable to SPECT as well as planar imaging. We will review these fundamentals of quantitative planar imaging as applied to Tc-99m sestamibi.

IMAGE STANDARDIZATION

Standardization of video and hard copy images is considered to be necessary for reproducible image interpretation. We use the Society for Motion Picture and Television Engineers (SMPTE) test pattern (Fig. 1) to fix the video contrast and brightness levels and adjust the film imager to achieve recommended values of film density for this test pattern. No arbitrary manipulation of background cutoff, contrast, brightness or film density is allowed. All images are made using the standardized settings. Background levels are set for a film density of 0.05 to 0.1 density units and maximum film density is set between 1.5 and 1.7. These density values are in accordance with the recommendations of the SMPTE Subcommittee on Recommended Practices for Medical Diagnostic Display Devices.

We also use a standardized intensity scale² designed to provide intuitively linear monochromatic conversion of count density into perceived brightness values. As the name implies, this standard "green scale" appears as a scale ranging from dark green through light green and finally to pure white. The color hue (shade of green) is constant but all 3 primary colors are actually used to achieve an expanded scale that is nonlinear in luminance but appears linear to the eye. The standard green scale is based on the Weber-Fetchner rule³ relating luminance to human mental perception of brightness. It is designed so

that image count density will be related linearly to perceived brightness value. A base hue of green is used because this allows the scale to be designed for simultaneous production of film or other hard copy. Green is also the primary video color in the center of the spectrum of human visual sensitivity. The standard green scale runs from 20 to 100% cathode ray tube beam intensity rather than starting at zero. This offset is used because both video tubes and film have a very nonlinear threshold near zero beam intensity or film exposure that causes inadvertent background suppression if the translation scale starts from zero intensity. This offset also allows imaging of background counts without imaging the video raster. This is accomplished by the use of a special color translation table that can be adapted for most modern computer video imagers.

PLACEMENT OF REGIONS OF INTEREST

Our program requires that the user place a rectangular region-of-interest (ROI) around the heart. These ROIs will be used for background subtraction, image registration and image rescaling. Each ROI should be placed so that the box just touches the heart on all sides (Fig. 2). The right ventricle (RV) should be included in the box. However, the part of the RV that extends above or below the left ventricle should not be included.

The user first places a ROI on the exercise image. The program then uses the same ROI on the rest image, allowing the user to reposition the box but not to change its size. Using the same box for rest images significantly reduces operator variability. (By quantitative measurement, the epicardial diameter of the heart does not change between exercise and rest images to such an ex-

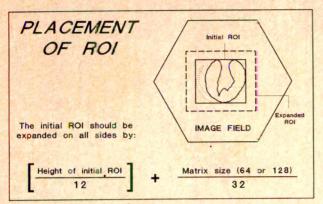


FIGURE 2. The region-of-interest (ROI) just touches the heart on all sides and includes the right ventricle. The ROI is then expanded so it lies in the background. The expansion depends on the matrix size and the height of the box in pixels. (Brackets denote that the result should be truncated.)

tent as to require resizing of the delineating box. Subendocardial ischemia often makes the "cavity" of the heart appear to shrink in the rest images. This is largely the result of redistribution into subendocardial regions and not primarily the result of persistent overt cardiac enlargement caused by exercise. The latter is less likely to occur with Tc-99m sestamibi since imaging is delayed for 30 minutes to 1 hour after exercise.) At any time, the user can instantly rescale the image to optimize placement of the ROI. This is especially useful for raw Tc-99m sestamibi images since the extracardiac activity may cause improper scaling. Once the ROI is placed, the program will automatically rescale the images to the hottest pixel inside the ROI.

Finally, the program automatically expands each ROI as indicated by Figure 2. This is done so that the ROI borders lie entirely in the background and do not include edge activity from the heart. Having the operator set the region to "touch" the heart and the computer to expand this region minimizes operator variability in setting the initial regions.

BACKGROUND SUBTRACTION

Background subtraction is essential to planar imaging both for valid quantification and for restoration of defect contrast adequate for visual assessment. Background for Tc-99m sestamibi images is more critical than for thallium-201 (Tl-201) because of the need to make close comparison of images after exercise injection with images after rest injection. The heart background ratio and shape of the extracardiac background is quite different at rest compared to exercise. A modification of the interpolative background algorithm used for Tl-2014 has been developed at our institution^{5,6} and was also recently tested at Yale by Koster et al.7 This modification does not significantly change the quantitative results of exercise and delayed redistribution imaging of Tl-201 and is thus interchangeable for Tl-201 imaging. In some cases, it will give improved results with resting injection of Tl-201 with or without dipyridamole because of improved separation of the high adjacent visceral activity. The modification should always be used with Tc-99m sestamibi imaging.

Background subtraction is the removal of the background, or more precisely the "tissue crosstalk," from the raw image. (Neither this method nor SPECT provides exact compensation for tissue crosstalk. A more detailed discussion of the rationale and limitations of this method appears in another report.8) For each image, a background is generated automatically from the smoothed image using the expanded boundary (Fig. 3). The background is then subtracted from the unsmoothed raw image. This leaves myocardial activity and a random pattern of residual counts outside the heart that reflect Poisson statistical noise. This pattern is useful for checking the correctness of the background plane.

With the modified algorithm, the expanded ROI may cross areas of intense extracardiac uptake, such as liver or lung, or local regions of abnormally low uptake, such as the edge of the chest wall or a pacemaker shadow, without propagating error into the background-subtracted myocardial image. This is accomplished by excluding the coldest 20% of boundary pixels as well as the hottest 50% in the computation of the average boundary value (variable V in Fig. 3).

RESCALING OF TECHNETIUM-99m SESTAMIBI IMAGES

Tc-99m activity in the viscera often exceeds that of the heart in Tc-99m sestamibi images. This normally causes the computer to scale image intensities to the extracardiac activity, which will cause erratic and suboptimal imaging of the heart (Fig. 4). Our computer program for quantitative Tc-99m sestamibi imaging automatically suppresses activity outside the heart if it becomes great enough to cause suboptimal imaging of the heart. This feature should be incorporated in all computer programs used for Tc-99m sestamibi imaging, whether planar or SPECT.

The computer rescales the raw image to the hottest pixel in the initial ROI (not the expanded ROI). Any

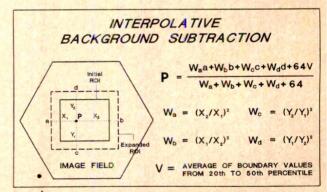


FIGURE 3. A rectangular background boundary is set by the operator to touch the edges of the heart. The computer program expands this boundary and generates a background reference plane according to the equations on the right. This equation is written so as to be independent of matrix size. The constant 64 is not related to the matrix but actually controls the steepness of the rolloff from boundary to background beneath the heart. Pixel counts on the expanded boundary are sorted from the lowest to the highest, and V is the average of all those values included from the 20th to the 50th percentile. ROI = region-of-interest.

pixel outside the initial ROI that is hotter than the heart will be automatically reset to 50% of the maximum heart pixel. This easily identifies hot extracardiac areas that have been scaled downward. The background-corrected images are also automatically rescaled in cases where the hottest pixel lies in the expanded ROI but not in the initial ROI.

IMAGE REGISTRATION

Accurate comparison of rest and exercise images for detection of redistribution requires that the images be in registration with each other. Image registration is the alignment of sequential images of a particular view (e.g., 45° left anterior oblique). The image registration techniques we have developed require no operator intervention and thus introduce no additional operator variability. These techniques ensure that rest and exercise profiles sample the same myocardial regions. They also enable the use of the flashback technique for the detection of subtle redistribution. This technique will be discussed later.

Initially, each background-corrected image is centered by finding the 2-dimensional centroid of the image (inside the expanded ROI) and then shifting the image so that the centroid is located in the center of the image matrix (Fig. 5). This is done for both the rest and exercise background-corrected images.

However, the rest image requires a more precise alignment with the exercise image than centering alone can provide. After centering, a cross-correlation technique is performed that aligns the rest image with the exercise

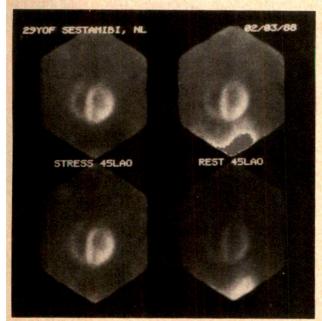


FIGURE 4. The stress and rest images on the *bottom* have been scaled normally by the computer. The intense visceral uptake in the rest image has caused suboptimal image display. The images above have been rescaled to the maximum count in the heart, a feature incorporated automatically in the quantitative analysis program. LAO = left anterior oblique; NL = normal.

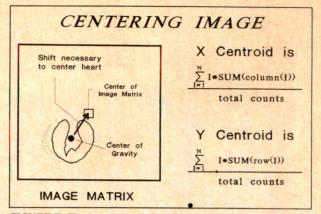


FIGURE 5. The background-corrected image is centered by computing the X and Y centroids that define the center of gravity. Then the image is shifted so the center of gravity now lies in the center of the image matrix. Any counts outside the expanded region-of-interest (not shown) are not included in the computations.

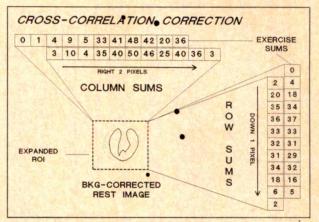


FIGURE 6. A final adjustment is made to the positioning of the background-corrected rest image by maximizing the cross-correlation coefficient with the exercise image. The computation is performed using the X (column) sums and the Y (row) sums inside the expanded region-of-interest (ROI). BKG = background.

image according to a 2-dimensional least-squares criterion. This is accomplished by iteratively translating the position of the rest image to maximize the cross-correlation coefficient with the exercise image (Fig. 6). Actually, the X and Y summed profiles are used instead of computing a pixel-by-pixel correlation coefficient. Again, only the elements in the expanded ROI are compared.

PROFILE GENERATION

After subtraction of the reference plane to compensate for tissue crosstalk and registration of the images to facilitate precise comparisons, quantification becomes the relatively simple matter of finding a convenient way of indicating image count density. In our view, the most basic and transparent way of doing this is to display count profiles across the heart.⁴ Four profiles will sample the myocardial count distribution adequately within the limitations of image resolution (each profile represents an

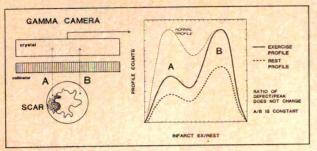


FIGURE 7. This figure defines a "persistent" defect. Consider the gamma camera image of a heart consisting of normal myocardium with normal tracer uptake and interdigitated scar with no tracer uptake. A profile of resulting activity is shown to the right. The ratio of activity in the defect zone (A) to normal zone (B) will remain the same in exercise (EX) and rest images because it is determined entirely by the geometry of the scar within the myocardium.

average of about a 1-cm-wide slice across the heart) and provide an intelligible display.

The circumferential profile method provides a more compact and dense single-curve display of counts sampled around the myocardial "rim" and allows the simple plot of a second profile indicating normal limits. Circumferential profile generation requires location of the center and edge of the myocardium and a computer search for some parameter, usually maximum count or integrated counts, along a radial profile from center to edge. The curve display also requires a reference angle, usually the apex, to be located by an operator. Consequently, there is more operator intervention and variability and a less obvious relation between the curves and myocardial images than for linear profiles. However, in our opinion, either method will provide an adequate and ultimately equivalent quantitative representation of myocardial activity. Either method facilitates standardization and reproducibility of image interpretation.

NORMAL DATABASE

Data from "normal" subjects may be incorporated into the computer program and indicated in the output as normal limits. The normal limits should be checked and modified as necessary by each user. Perfusion defects and especially redistribution should be confirmed by quantitative criteria. Computer results should always be subject to interpretation and confirmation by a competent specialist. Many normal variants can be easily recognized by an interpreter but not by the computer. Gender-specific normal limits have been suggested to cope with breast attenuation artifacts. However, in our experience, attenuation artifacts are so varied that it may be better to use a single normal standard and judge by the image pattern and body habitus if a region of reduced activity was caused by attenuation.

QUANTITATION OF REST REDISTRIBUTION

Redistribution must be defined before it can be quantitatively determined. The definition we use works equally well for Tc-99m sestamibi and Tl-201. As shown in

Figures 7 and 8, a persistent defect is one in which the ratio of activity in defect to normal myocardium is constant. "Rest redistribution" is defined by a statistically significant change in this ratio when comparing exercise with rest images. This definition is identical to our conventional definition of redistribution with Tl-201 delayed images. However, to reduce confusion, we would refer to the latter as "delayed redistribution." In either case, the terms denote literally a change of tracer distribution within the myocardium. Myocardial washout rate after an intravenous systemic injection of Tc-99m sestamibi is minimal and is not analyzed. This definition does not depend on absolute washout rate.

The standard computer display of a normal Tc-99m sestamibi study is shown in Figure 9 (A and B). A raw image is displayed next to the image after background subtraction has been performed. Profiles appear below the image. Exercise profiles are scaled so the maximum value is at full scale. Rest profiles are scaled with the maximum value at 75% full scale to facilitate comparison when exercise and rest profiles are overlapped. Figure 9C shows an alternative "survey" screen that displays all 6 images simultaneously.

FLASHBACK DISPLAY

The detection of subtle redistribution, which often indicates residual viability within an infarct zone, requires very close comparison of defect ratios between exercise and rest images. This can be done by producing functional images that represent ratio maps. However, these are completely abstract images that lack the transparency to be very robust as clinical tools. We have developed an alternative method that has been more enthusiastically accepted by clinicians. As previously stated, the exercise and rest background-corrected images have been brought into registration so that they match pixel for pixel. Next, these images are each scaled to their maximum count and are then displayed so the alternate image can be instantly flashed back on the screen in the same position. Thus, if the tracer distributions of both images are unchanged, the flashback image will be identical except for statistical noise. If there has been redistribution in a myocardial segment, that segment will exhibit a

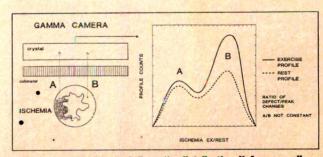


FIGURE 8. This figure defines "redistribution." Assume all myocardium is viable but a transiently ischemic region has caused reduction of myocardial uptake in the defect zone (A) compared to a normally perfused zone (B). In rest images (or in delayed redistribution images) the ratio of A/B will change toward unity. EX = exercise.

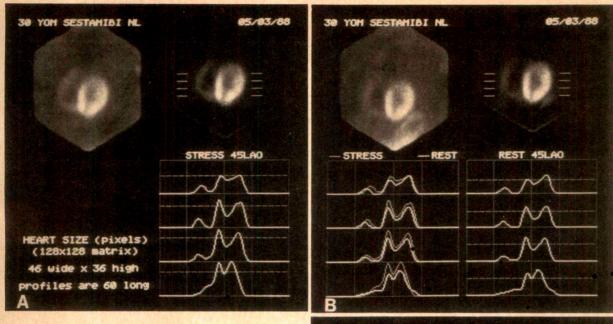
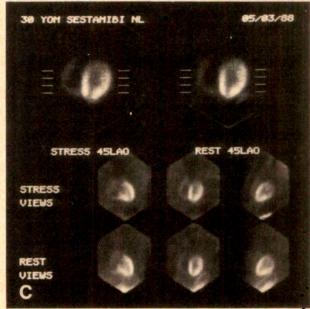


FIGURE 9. A and B, the normal display screens for visual and quantitative analysis of the 45° left anterior oblique (LAO) views. C, an optional screen showing all 6 images simultaneously below while allowing a choice of 2 normal-sized processed images for display above. NL = normal.



sudden shift of intensity relative to the remainder of the image during flashback. This allows very sensitive visual identification of regions of redistribution while maintaining standard anatomic images for the interpreter rather than functional abstractions.

GATED IMAGE ACQUISITION

Standard 16-frame MUGA acquisition is used for Tc-99m sestamibi imaging. Gated images are then viewed in cine mode. Our program for perfusion image processing recognizes the gated images and automatically sums them into a single static image for quantitative analysis. The nonzoomed 10-inch camera field of view is nearly optimal as it will encompass the entire heart and enough area around the heart from which to derive the background reference plane. When a 15-inch camera is used,

we recommend a zoom of about 1.5× to maintain a 10-inch total field of view.

QUANTITATION OF SPLIT DOSE

Tc-99m sestamibi does not significantly redistribute within the first few hours of injection. Consequently, an injection given at rest must be compared with an exercise injection or one given after dipyridamole infusion. This can be done the same day¹⁰ using a small dose for the initial injection followed by a much larger dose. Alternatively, the first injection can be subtracted along with the background. This procedure is facilitated by the computer program described since initial and delayed images are automatically brought into precise registration and background subtraction is performed routinely. Modification to include the first image as part of the background is

simple. This technique will be evaluated to determine the optimum way of splitting the total dose to obtain 2 studies in a single day.

DUAL ISOTOPE

TI-201 has a theoretical advantage as a viability marker because delayed redistribution can occur if there is intact cell membrane function even in a chronic lowflow state. Moreover, the possibility of simultaneous dual isotope imaging is intriguing. If Tc-99m sestamibi were injected during stress and Tl-201 injected after stress, a single delayed image performed so as to determine the ratio of Tc-99m to Tl-201 activity could at once determine both perfusion and viability. By virtue of being accumulated simultaneously, both images would be in exact registration, at exactly the same angle and with exactly the same overlying body tissue. Comparative sampling of identical myocardium would be automatic. This would obviate many imaging difficulties. The technical problems of spectral decomposition of Tc-99m and Tl-201 activity are substantial, particularly due to the fact that Compton scatter contributing to "spill-up" and "spill-down" fractions will be dependent on body habitus. Devising analytic methods to compensate for this will be challenging, but the potential advantages make this worthy of investigation.

CONCLUSION

The basics of computer processing discussed herein include optimizing and standardizing the images, separation of myocardial activity from background, image registration and precise sampling for comparing initial and delayed images, and viability detection based on a rational quantitative definition of redistribution. This quantitative approach places reproducibility as a high priority because reproducible standards must exist for a test to have broad acceptance. The computer is used as an essential tool for measurement but not to displace clinical wisdom and logical subtlety. These principles are not confined to planar imaging or a particular method or tracer. For the most part, this represents common engineering principles applied to perfect the art of myocardial perfusion imaging into a science or at least a craft. Our experience leads us to conclude that, whether by planar or SPECT, perfection of the method will lead to greater gains in clinical efficacy than pursuit of technological invention.

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Technical Aspects of Myocardial SPECT Imaging with Technetium-99m Sestamibi

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Most reports to date using single photon emission computed tomography (SPECT) with technetium-99m (Tc-99m) sestamibi have used acquisition parameters that were optimized for thallium-201. To fully utilize the superior imaging characteristics of Tc-99m sestamibi, there is a need to optimize the technical aspects of SPECT imaging for this agent. Performance can be enhanced through the careful selection of optimal radiopharmaceutical doses, imaging sequences, acquisition parameters, reconstruction filters, perfusion quantification methods and multidimensional methods for visualizing perfusion distribution. The current report describes theoretical considerations, phantom studies and preliminary patient results that have led to optimized protocols, developed at Emory University and Cedars-Sinai Medical Center, for same-day reststress studies, given existing instrumentation and recommended dose limits. The optimizations were designed to fit a low-dose-high-dose rest-stress same-day imaging protocol. A principal change in the acquisition parameters compared with previous Tc-99m sestamibi protocols is the use of a highresolution collimator. The approach is being developed in both prone and supine positions. A new method for extracting a 3-dimensional myocardial count distribution has been developed that uses spherical coordinates to sample the apical region and cylindrical coordinates to sample the rest of the myocardium. New methods for visualizing the myocardial distribution in multiple dimensions are also described, with improved 2-dimensional, as well as 3- and 4-dimensional (3 dimensions plus time) displays. In the improved 2-dimensional display, distance-weighted and volume-weighted polar maps

are used that appear to significantly improve the representation of defect location and defect extent, respectively. The protocols established and the methods developed for acquisition, quantification and display of Tc-99m sestamibi SPECT should provide improved image quality and accuracy, compared to current thallium-201 and Tc-99m sestamibi studies reported to date.

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echnetium-99m (Tc-99m) sestamibi offers physical characteristics that make it a superior imaging radiopharmaceutical compared to thallium-201 (Tl-201). The higher energy gamma rays emitted by Tc-99m photons (140 keV) compared with Tl-201 photons (80 keV) are significantly less affected by Compton scatter and attenuation as they traverse the patient. Our calculations indicate that the acquired Tc-99m sestamibi myocardial count distribution is generated by radiation that, on the average, undergoes 50% less Compton scatter and 20% less attenuation than Tl-201. This reduced interaction within the patient results in better inherent imaging characteristics and a lower radiation exposure to the patient per millicurie of tracer injected. In addition to exhibiting lower radiation absorption, the significantly shorter half-life of Tc-99m (6 hours) versus Tl-201 (73 hours) permits administration of a much higher dose of radioactivity, resulting in a higher photon flux and a significantly higher counting rate. Moreover, the higher energy Tc-99m gamma rays, once absorbed by the sodium iodide crystal of the gamma camera, emit significantly more light, allowing for better positioning by the photomultipliers and a higher inherent spatial resolution.

With respect to single photon emission computed tomography (SPECT), the superior imaging characteristics of Tc-99m sestamibi compared to Tl-201 can be fully realized only if the technical aspects of myocardial SPECT are optimized. These technical aspects include radiopharmaceutical dose, imaging sequence, acquisition parameters, reconstruction filters, perfusion quantification methods and multidimensional methods for visualizing the perfusion distribution. The current report describes the approach to optimization of the Tc-99m sestamibi SPECT studies undertaken as a combined effort of the nuclear cardiology sections of Emory University and

Cedars-Sinai Medical Center.

From Emory University School of Medicine, Atlanta, Georgia; Cedars-Sinai Medical Center, Los Angeles, California; Georgia Institute of Technology, Atlanta, Georgia; and St. Luke's Medical Center, New York, New York. This study was supported in part by grants RO1-HL42052 and RO1-HL41628 from the National Institutes of Health, Bethesda, Maryland, as well as a grant from E. I. du Pont de Nemours & Co., North Billerica, Massachusetts.

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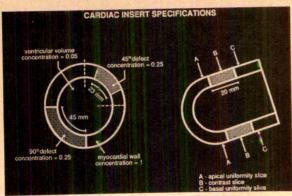


FIGURE 1. Cardiac phantom configuration used to optimize imaging protocol. Note location and relative concentration of the 2 defects used for determining defect contrast. The relative myocardial wall concentration of 1 corresponded to approximately 6 µCi/ml.

METHODS

Acquisition protocol: We have used a same-day imaging protocol involving a low-dose resting study followed by a high-dose stress study. This approach allows the studies to be completed in 1 day, yields high image quality for the more important stress study and circumvents the reported problem of difficulty in assessing defect reversibility when the stress study is performed first.1

Patient preparation: Doses chosen were optimized within the limits of a 30 mCi total dose on day 1 imposed by the proposed package insert, which is under evaluation by the Food and Drug Administration. The standard doses of Tc-99m given for a patient weighing 70 kg are 8 mCi for the resting study and 22 mCi for the stress study. In our experience, doses smaller than 8 mCi for the resting studies are associated with inadequate image quality. For a heavier patient, these doses are scaled up to a maximum of 9 mCi and 25 mCi, respectively. Patients are given 236.5 ml whole milk 15 minutes after receiving the injected dose to facilitate tracer clearance from the gallbladder. Imaging begins 1 hour after the injection for the resting study, and 30 minutes after the injection for the stress study. The earlier post-stress imaging period was selected to minimize the effect of possible minimal redistribution of the tracer. Standard symptom-limited treadmill exercise is performed using the Bruce protocol with the injection of Tc-99m sestamibi at the peak of exercise and continuation of exercise for an additional minute. A delay of 3 to 4 hours between the studies allows the radioactivity from the resting study to decay 29 to 37% before the stress study is begun. The 4-hour interval is preferred because of the additional reduction in background counts and our observations that this interval offers optimum patient throughput.

Acquisition parameters: Optimization of the acquisition parameters for single-detector camera systems was performed using phantom studies. The contrast of simulated defects and uniformity of normal slices were used as parameters for evaluating imaging characteristics. Maximal-count circumferential profiles extracted from a short-axis slice cutting through 2 defects were used to

measure defect contrast. The maximum counts in the profile were identified as well as the minimum counts for the 2 defects. Contrast for each defect and each imaging configuration was determined as follows: contrast (maximum counts - minimum counts)/maximum counts.

Maximal-count circumferential profiles extracted from 2 short-axis slices cutting through regions of homogeneous tracer distribution toward the base and toward the apex were used to measure uniformity of normal slices. The mean counts of the circumferential profile (as well as the standard deviation) were calculated for each of the 2 normal slices in each imaging configuration. Uniformity of these slices was determined in the following manner: uniformity = standard deviation/mean

The phantom used for optimizing the acquisition parameters consisted of an elliptical water bath (30.5 cm major axis, 22 cm minor axis, 18.6 cm height) with simulated cardiac, lung and spine inserts. The 2 lung inserts were made of Styrofoam in the shape of lungs surrounding the heart. The spine insert consisted of a 5 cm diameter plastic cylinder filled with bone meal. The cardiac insert consisted of a plastic chamber simulating the left ventricular chamber surrounded by a 1-cm-thick plastic chamber simulating the left ventricular myocardium. Two smaller fillable chambers (1 cm thick, 2 cm long) were used to simulate hypoperfused defects. All chambers were filled according to the relative concentrations shown in figure 1 simulating the count distributions measured from patient studies with 25 mCi of Tc-99m sestamibi. All acquisitions were completed while keeping the total time of acquisition constant after correcting for physical decay of Tc-99m between studies.

The following parameters were evaluated: (1) symmetric versus asymmetric energy windows; (2) high-resolution versus all-purpose collimators; (3) circular versus elliptical camera orbits; (4) 180° versus 360° camera orbits; (5) 64 × 64 versus 128 × 128 matrices; and (6) number of projections.

Quantitative protocols are being developed for both the prone and supine positions. The time per projection has been set at 25 seconds for the resting study and 20 seconds for the exercise study. These time settings limit total acquisition time to ≤30 minutes, which in our experience represents the maximal time routinely well tolerated by patients. The exercise study is electrocardiogramgated using 8 frames for the cardiac cycle.

Reconstruction protocol: The acquired projections of the rest and exercise studies were corrected for radioactive decay from the beginning of image acquisition.

Reconstruction: The transaxial tomograms were reconstructed as slices 1 pixel (6.4 mm) thick using a Ramp filter and were reoriented along the vertical and horizontal long axes and the short axis of the left ventricle. Once reoriented, the 6.4-mm slices were combined 2 frames at a time and increased by 1 frame each time to yield a thickness of 12.8 mm every 6.4 mm of length. This reframing produced slices with twice the count density/ pixel with equal spatial resolution in all directions.

Filter selection: A filter evaluation was conducted to determine the optimal two-dimensional, preprocessing filter parameters for Tc-99m sestamibi imaging. The previously described phantom containing 2 defects was used for this evaluation. The optimum filter selected was that which supplied the best contrast in the tomogram containing the 23-mm and 45-mm defects with an acceptable uniformity in the tomogram containing uniform activity. These studies were acquired using a 64 × 64 matrix and low-energy all-purpose (LEAP) collimator as well as a 128 × 128 matrix and high-resolution collimator. Butterworth and Hamming filters were studied.

Quantitation and display: Conventionally, maximal-count circumferential profiles are routinely extracted from short-axis slices^{2,3} and vertical long-axis slices² to represent the 3-dimensional myocardial tracer distribution. These profiles are subject to partial-volume effects, particularly in the apical region. Thus, a new technique has been developed to generate count profiles from a hybrid, 2-part, 3-dimensional sampling scheme of stacked, short-axis slices.⁴ This new technique ensures a radial sampling that is perpendicular to the myocardial wall at all points and provides a more accurate representation of the perfusion distribution. The need for subjectively defining the apex also is avoided.

Three-dimensional sampling: Maximal-count circumferential profiles are automatically generated from the short-axis slices using a 2-part sampling scheme (Fig. 2). First, the apical cap is identified as stacked, short-axis slices that form a hemisphere; i.e., the radius (mm) of the top slice of the stack is equal to the depth (mm) of the stack (Fig. 2, left). The apical cap then is sampled in a spherical coordinate system as seen in the bottom right diagram of Figure 2. Each point in the profile represents the maximum counts/pixel encountered along the radius of search for each phi and theta angular sample. The remaining portion of the myocardium is relatively cylindrical in shape and is sampled slice-by-slice using a cylindrical coordinate system (Fig. 2, top right).

The radii corresponding to the distance from the center of reference to the location of the extracted maximal counts are filtered in both depth and angle using a 3 × 3 low-pass filter kernel. The filtered radii then are assembled as circles and transformed into Cartesian coordinates. These coordinates, along with their associated maximal counts, are recorded and used to generate 2-, 3- and 4-dimensional visualization models.

Two-dimensional polar maps: One of the more popular forms of visualizing myocardial perfusion is by using 2-dimensional polar maps. 2.3 These polar maps are constructed by mapping sequential maximal-count circumferential profiles, extending from the apex to the base, into successive rings on the polar map. The apex is mapped into the center of the polar map and the base is mapped into the periphery of the polar map. A standard 2-dimensional polar map for an abnormal phantom study is shown in the top right of Figure 3. The vertical long-axis and short-axis slices corresponding to a cardiac phantom with defects at the anteroapical and anterolateral regions are shown in Figure 4. Note that the standard

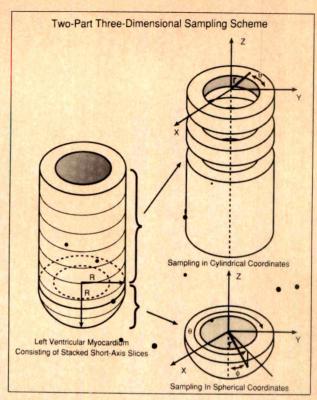


FIGURE 2. Three-dimensional hybrid sampling scheme. This scheme for extracting the myocardial tracer distribution was designed to search for the maximum counts along a radius perpendicular to the myocardial wall, to eliminate partial-volume effects.

polar map does not accurately represent the extent of the anteroapical defect seen on the slices. This discrepancy is due to sampling errors encountered in apical slices as a result of the method used in generating the polar maps.

Two new polar maps have been developed to use the more accurate information that is extracted from the short-axis slices by the 2-part sampling scheme described earlier.4 The first polar map is called the "distanceweighted polar map" and is constructed so that every ring in the polar map is of the same width. The width for a given study is determined by dividing the radius of the polar map by the total number of sampled segments (spherical rings + cylindrical slices). The phantom study contained 28 sampled segments (11 spherical rings and 17 cylindrical slices). The polar map was drawn at a resolution of 256 × 256, with a radius of 128 pixels, and had rings that were 4.57 pixels wide. The raw distanceweighted polar map for the phantom study is shown in the top right of Figure 5. This polar map is similar to that currently used with Tl-201 scintigraphy in the Cedars-Sinai Medical Center approach with the difference being in the method of sampling the apex spherically using the short-axis rather than the vertical long-axis tomograms.

The second polar map is called a "volume-weighted polar map" and is constructed in 2 parts. First, the volume of the apical cap is determined, and its percentage of the total volume is calculated. The apical cap then is mapped so that the area of the apical cap is the same

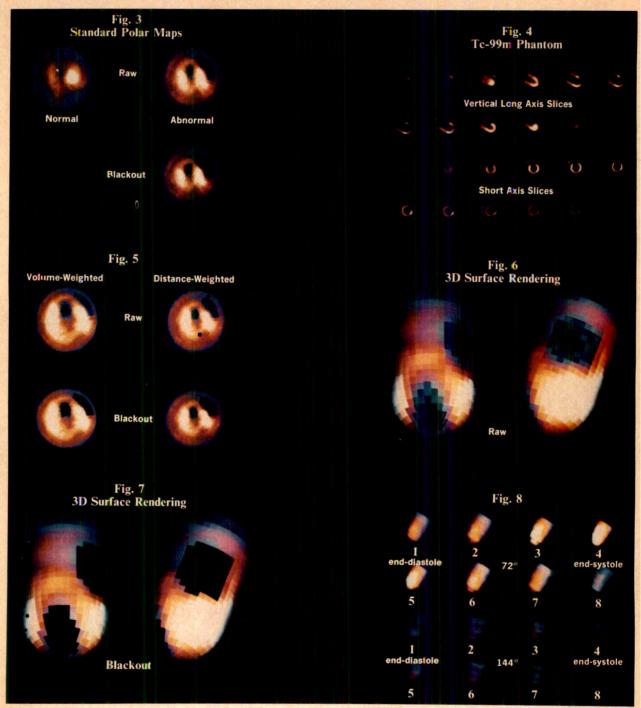


FIGURE 3. Standard raw and blackout polar maps for the normal and abnormal phantom studies.

FIGURE 4. Vertical long-axis slices and short-axis slices from the abnormal phantom study. Tc-99m = technetium-99m.

FIGURE 5. Volume-weighted and distance-weighted raw and blackout pôlar maps for the abnormal phantom study.

FIGURE 6. Three-dimensional surface rendering of the raw abnormal phantom showing the extent and location of the 2 defects using the model that represents the true shape of the myocardium. The model has been tilted at 30° to simulate the position of the heart within the thorax. The projection on the left is an anterior view (or viewed from 0°); the projection on the right is an anteriorateral view (or viewed from 45°).

FIGURE 7. Three-dimensional surface rendering of the blackout abnormal phantom, with 30° tilt: left is an anterior view; right is an anterior view;

FIGURE 8. Three-dimensional model of a multiple-gated patient single photon emission computed tomography (SPECT) study shown from 2 different projections. Note that the eighth frame of both projections has lower counts than surrounding frames due to rejection of ectopic heartbeats.

percentage of the total area of the polar map as the volume of the apical cap is of the total volume of the myocardium. Each ring within the apical cap is constructed of equal width. For the remainder of the myocardium, the area of each ring is proportional to the volume of the corresponding slice. The resultant raw volume-weighted polar map is shown in the top left of Figure 5. This volume-weighted polar map makes the relative 2-dimensional area of a defect equal to the relative 3-dimensional volume of that defect (i.e., it corrects for spatial distortions inherent in displaying a 3-dimensional volume 2-dimensionally and also takes into account variations in slice mass from apex to base).

These 2 new polar maps were tested in phantom studies and patient studies. For the phantom studies, both a normal phantom and an abnormal phantom were used. The inferoseptal wall of the 2 phantoms (between 6 o'clock and 9 o'clock on the polar maps) was used to normalize the 2 studies because it was the most uniform in tracer concentration. This normalization process involved summing all of the counts in the inferoseptal wall, excluding the apical cap and the last 3 cylindrical slices, and dividing the sum from the normal phantom by the sum from the abnormal phantom. The counts in the abnormal phantom then were multiplied by the factor resulting from the normalization calculation. Blackout maps were then generated where the extent of the abnormal regions with reduced counts was highlighted in black. These blackout maps corresponding to the standard, distance-weighted and volume-weighted polar maps were calculated by setting to 0 all pixels in the polar maps that were below the counts in the normal map, minus 28%. This 28% threshold, which was used to identify the extent of the abnormal regions with reduced counts, was determined by calibrating the defect volume measured by water displacement to the defect volume blacked-out in a true 3-dimensional representation of the phantom. A standard blackout map is shown in the bottom right of Figure 3. The volume-weighted and distance-weighted blackout maps are shown in the bottom left and bottom right, respectively, of Figure 5. The area that each blacked-out defect occupied, as a percent of the total area of the polar map, was compared with the percent of the total volume that each defect occupied, as measured by water displacement. The ratio of the blacked-out area of the 2 defects also was compared with the ratio of the volume of the 2 defects.

Ten patient cases also were used for evaluating the new polar maps. For each case, 3 polar maps were generated: standard, distance-weighted and volume-weighted. Two expert observers were asked to subjectively rank the 3 polar maps from best to worst, in terms of the accuracy of defect location and size, and apical perfusion distribution, compared with the patient's short- and vertical long-axis slices.

Three-dimensional visualization: We currently are using 2 models for visualizing perfusion information in 3 dimensions: an ellipsoidal model; and a model that more closely represents the true shape of the myocardium. The ellipsoidal model is a generalized ellipsoid that offers the advantage of being a standardized shape from patient to

patient, much like the 2-dimensional polar maps are a standardized shape from patient to patient. The true 3-dimensional model uses the filtered and transformed Cartesian coordinates of the maximal-count circumferential profile points to represent the myocardium and offers the advantage of more accurately depicting the patient-specific shape of the myocardium. Both models can be rendered using the raw profile map or the blackout profile map (Figs. 6 and 7).

The 3-dimensional models are generated using MAX, a modeling software package developed at the Georgia Institute of Technology.5 The models are built using hermite patches, which are surface descriptors in MAX, consisting of 4 vertices with a normal vector at each vertex. The patch passes through the 4 vertices and forms a cubic spline surface defined by the vertices and the vertex normals. The points on the patch surface are located by interpolating the vertex normals and fitting a cubic polynomial through the adjacent points and the interpolated normal vectors. One hermite patch is created for each of the maximal-count profile points. The vertices and vertex normals are based on the equation of an ellipse for the ellipsoidal model and on the filtered and transformed Cartesian coordinates of the maximal-count points for the true 3-dimensional model. The color of each patch is assigned based on the counts in the raw profile map for the raw 3-dimensional model, or the blackout profile map for the blackout 3-dimensional model. MAX is used to render the model as a smooth-shaded surface. viewed from any orientation in space. Each point in the myocardial surface is color-coded according to the count density at that location and shaded according to the angle that an imaginary light source makes with the surface and the observer's frame of reference. Optimal rendering requires the use of 24 bits/pixel to generate a display that truly appears 3-dimensional to the eye. A cine loop can be created by rendering multiple projections of the model over 360° and playing back the projections at any desirable frame rate.

Four-dimensional visualization: The true 3-dimensional model can be extended to 4 dimensions (3 dimensions plus time), where the color of each patch in the model, corresponding to count density, is proportional not only to tracer concentration, but also to wall thickness. The temporal dimension is obtained by electrocardiographic gating of the tomographic acquisition. A multiple-gated tomographic perfusion study is acquired in much the same way as a static acquisition, except that the cardiac cycle is divided into 8 segments. Each of these segments is treated as 1 static acquisition. When the gated study is completed, there are 8 separate static studies corresponding to the 8 segments of the cardiac cycle. These 8 studies then are built into 3-dimensional models as previously described, with the counts in each study normalized to the maximal count among the 8 studies. To create a cine loop of the gated perfusion data, all 8 segments of the cardiac cycle are rendered for each of 10 projections of the model over 360°, giving a total of 80 projections at a resolution of 256 × 192 each. The 8 segments of a gated patient study for 2 different projections are shown in Figure 8.

TABLE I Defect Contrast and Normal Slice Uniformity Measured for Different Acquisition/Reconstruction Protocols

		Con	trast			Unifo	rmity	
	23	mm	45 1	mm	Ap	ex	Ва	ise
Camera Orbit	64	128	64	128	64	128	64	128
Circular 180°	0.73	0.84	0.56	0.79	0.10	0.12	0.07	0.12
Elliptical 180°	0.62	0.75	0.76	0.86	0.15	0.26	0.13	0.14
Circular 360°	0.59	0.78	0.69	0.79	0.07	0.08	0.06	0.10
Elliptical 360°	0.50	0.67	0.74	0.84	0.07	0.09	0.09	0.10

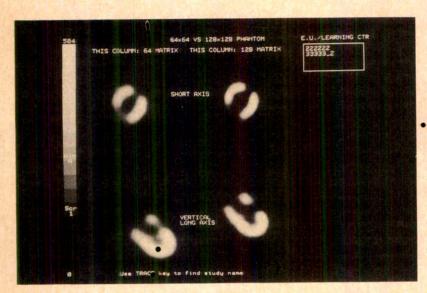


FIGURE 9. Short-axis and vertical long-axis tomograms of the phantom configuration shown in Figure 1. Left: tomograms imaged using an all-purpose collimator and 64×64 projections. Right: tomograms obtained using a high-resolution collimator and 128×128 projections. Note the higher defect contrast and thinner myocardium yielded by the use of the high-resolution, 128×128 methodology.

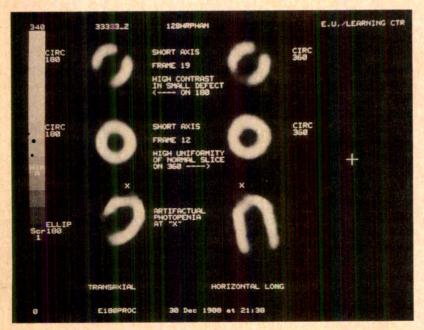


FIGURE 10. Comparison of defect contrast and normal slice uniformity of the phantom configuration shown in Figure 1, acquired by using different camera orbits. Note the higher defect contrast of the short-axis slice obtained by imaging using a circular (CIRC) 180° orbit. The higher uniformity of the normal slice was obtained by using a circular 360° orbit. Note the photopenic artifact generated by using an elliptical (ELLIP) 180° orbit.

RESULTS

Acquisition parameters: The results of the phantom studies with respect to acquisition parameters are summarized, in part, in Table I and Figures 9 and 10. The parameters chosen as optimal for the rest and exercise count-density studies were a 20% symmetric energy win-

dow, a high-resolution collimator and a circular 180° orbit using 64 projections from a 45° right anterior oblique (RAO) to a 45° left posterior oblique (LPO) orientation. The use of a high-resolution collimator is particularly important because it provides a more constant resolution response with depth than the all-purpose

collimator, particularly relevant for circular myocardial SPECT. The superior spatial and contrast features at depth of the high-resolution collimator are shown in Figure 9. Although the circular 360° orbits yielded the best overall uniformity in normal slices, the circular 180° orbits provided higher contrast of small lesions and higher count density (Fig. 10, Table I). For this experimental setup, the elliptical 180° orbits produced an apical photopenic artifact.

The results of the phantom studies suggested initially that the 128 × 128 matrix acquisition was preferable to the 64 × 64 matrix (Fig. 9). However, subsequent investigations with patient data demonstrated the need for a lower cutoff frequency for the preprocessing filters⁷ to maintain consistently high image quality in a wide variety of patient sizes. This change reduced the degree of improvement of image quality between the 128 and 64 matrices. Moreover, because multiple-gated SPECT acquisition may be desirable, requiring additional computer disk space that may not be readily available for 128 × 128 matrices, we concluded that 64 × 64 projections provide the most effective overall matrix configuration. Our final acquisition protocols are summarized in Tables II through IV.

Reconstruction: The new reconstruction methodology applied to 64 × 64 projections is compared with the methodology previously reported for 128 × 128 images in Table I. Note that the new methodology improves uniformity at a loss of contrast, consistent with the need to guarantee high image quality in studies with limited counts, such as in resting studies of heavier patients.

Filter selection: The filters evaluated and their cutoffs are listed in Table V. The Butterworth filter, cutoff 0.72 cycles/cm and order 5, was found to be optimal for the 64 × 64 LEAP study. The Butterworth filter demonstrated improvement in contrast compared to the Hamming filter over the entire range of cutoffs evaluated. The Butterworth filter applied to a 64 × 64 phantom study with high-resolution collimation demonstrated even better contrast (0.73, Table I) than the 64 × 64 LEAP study (0.63, Table V) even though a lower cutoff frequency was used.

The cutoff of the Butterworth filter had to be lowered to reduce the higher frequencies associated with clinical data. Projection data were pre-filtered using a 2-dimensional Butterworth filter. Different filter parameters were

TABLE II Patient Protocol				
	Rest	Exercise		
Dose	8–9 mCi 236.5 ml milk	22–25 mCi 236.5 ml milk		
Position Delay time (intervals)	Prone	Prone		
Injection → imaging Rest → stress	1 hour	30 minutes 3–4 hours		

	Rest	Exercise
Energy window	20% symmetric	Same
Collimator	High resolution	Same
Orbit	180°, circular	Same
No. of projections	64	Same
Matrix	64 × 64	Same
Time/projection	25 seconds	20 seconds
Total time	30 minutes	25 minutes
ECG gated •	No	Yes
Frames/cycle	· ·	8
R-to-R window (%)	100	100

	Rest	Exercise
Preprocessing		
Projections	Decay-corrected	Same
Filter	2D Butterworth	Same
Definition		
General Electric		
Cutoff frequency	0.4 cycles/cm	0.52
Power	10	5
Siemens		
Cutoff frequency	0.5 Nyquist	0.66
Order	5	2.5
Reconstruction		
Filter	Ramp	Same
Oblique slices		
Thickness	12.88 mm	12.88 mm
Increment	6.4 mm	6.4 mm

		Con	trast			
Filter/Cutoff	64	× 64	128	× 128	Unit	formity
(cycles/cm)	23 mm	45 mm	23 mm	45 mm	64 × 64	128×128
Butterworth/0.64	0.55	0.60	0.84	0.81	0.10	0.10
Butterworth/0.72	0.63	0.69	0.86	0.83	0.11	0.11
Butterworth/0.80	0.64	0.70	0.86	0.83	0.12	0.12
Hamming/0.64	0.56	0.50	0.64	0.63	0.07	0.07
Hamming/0.72	0.55	0.54	0.66	0.66	0.09	0.08
Hamming/0.80	0.58	0.57	0.72	0.67	0.10	0.12

TABLE VI Defect Maps Used	Size Determ	ination for t	he Different Polar	
	% of Myo	cardium	Ratio of	
Polar Map Type	Apical Defect	Lateral Defect	Apical to Lateral Defect	
Actual phantom	3.03	4.59	0.66	

7.86

6.38

5.82

1.55

1.77

3.46

Standard

Distance-weighted

Volume-weighted

0.20

0.28

0.60

used for the different count densities of the rest and exercise studies to generate tomograms of comparable image texture. For the rest study, the applied filter had a cutoff frequency of 0.4 cycles/cm with a power factor of 10. For the exercise study, the applied filter had a cutoff frequency of 0.52 cycles/cm and a power factor of 5. Images were found to be smoother with a lower cutoff frequency and a higher power factor. These 2 filters have a matched response for the lower frequencies that define the myocardium. However, the filters have a different response at the higher frequencies to account for the differences in statistical noise between the resting and exercise studies. These filters are defined using dimensions found in the General Electric Starcam systems. Care must be taken when translating these units to those of different manufacturers, which might use different dimensions. For example, on the Siemens systems, these same filters are defined differently (Table IV).

Quantitation and display: Two-dimensional polar maps: The results obtained from the evaluation of the phantom defect sizes by the various polar maps are listed in Table VI, along with the results from standard polar maps and the actual values measured from the phantom studies. Note that the volume-weighted polar map provides the best representation of the actual volume of the defects. The expert observers ranked the distance-weighted polar map as the best for determining defect location, and the volume-weighted polar map as the best for determining defect size. Both maps were ranked equally well for assessing apical distributions. The standard polar map ranked the lowest in all 3 categories. Although the distance-weighted and volume-weighted polar maps offer improvement over standard maps in characterizing perfusion defects, distortions still exist in the size, shape and location of perfusion defects. These distortions are inherent in mapping 3-dimensional data into 2 dimensions, although the distortions can be reduced greatly when the perfusion data are visualized in 3 dimensions.

Three-dimensional visualization: Two projections of the raw 3-dimensional model are shown in Figure 6, and the corresponding projections of the blackout 3-dimensional model for the phantom are shown in Figure 7. Both models are tilted at 30° to simulate the position of the heart within the thorax. In each figure, the projection on the left is shown from an anterior view of the heart (or viewed from 0°), and the projection on the right is shown from an anterolateral view (or viewed from 45°).

DISCUSSION

In this project we have established what we currently consider the optimal protocols for acquiring and reconstructing myocardial SPECT studies with Tc-99m sestamibi, given existing instrumentation and dose recommendations in the proposed package insert. The optimizations were constrained to fit a strategy of using a low-dose resting study and a high-dose exercise study imaged with a single detector system. This approach allows the combined study to be completed in the same day. Although a stress study first would be more similar to current stressredistribution Tl-201 protocols and thus more convenient, for Tc-99m sestamibi this approach has major drawbacks. The lower exercise dose would result in less than ideal quality due to low count statistics, thereby reducing the potential for resolving stress perfusion defects, probably the most important reason for performing the study. Second, the lower stress dose would probably be inadequate for first-pass exercise ejection fraction studies even with dedicated first-pass cameras. Third, early data have suggested that the perception of defect reversibility is diminished with this approach due to uneven stress distribution on which the resting study is later superimposed. The same parameters may be used either for a single-day protocol or applied to a 2-day protocol. An important aspect of these optimized protocols has been the decision to exchange half of the abundant counts from Tc-99m sestamibi for the use of high-resolution imaging. This exchange results in higher resolution and less change in resolution with depth compared with previous protocols used to image Tl-201.

Supine images have been associated with basal inferior and inferoseptal defects similar to those associated with Tl-201. A prone Tc-99m sestamibi acquisition protocol reduces the basal artifact. Artifactual anterior wall perfusion defects are occasionally observed in the prone position; these defects, however, are usually distinguishable from true defects by not conforming to a typical coronary pattern. To fully realize the benefits of cardiac tomography in the prone position, the effects of attenuation due to the scan table need to be considered, particularly to reduce potential attenuation in the anterior wall. One approach to overcome table attenuation is use of a table with a cutout for the cardiac region.8 Another approach being explored is correction for the photon attenuation due to the scan table. The approach consists of tomographic transmission imaging using a Tc-99m pertechnetate-filled flood source imaged through a scanning table and in free air. Images composed of count ratios (table/no table) at each pixel position for each projection are created, resulting in a correction file of 48 frames that corresponds to the part of the scan subject to table attenuation. Correcting attenuation improves phantom images both visually and statistically. However, it is unknown whether correcting for scan table attenuation is clinically significant. Studies currently in progress will address this question. In addition, the use of thinner scan tables designed to further reduce table attenuation might circumvent the need for this correction.

Since either position can be associated with attenuation artifacts, and since some patients can tolerate one but not both of the positions, it will be necessary to develop normal limits for quantitative Tc-99m sestamibi SPECT in both prone and supine positions.

In this study, the combined counts from all 8 frames throughout the cardiac cycle were used for the quantification of regional myocardial perfusion. We have observed, however, that cine display of the myocardial Tc-99m sestamibi distribution throughout the cardiac cycle is useful in identifying imaging artifacts. This type of display also has been valuable for assessing wall motion and thickening, which are factors that can help determine myocardial viability. Our previous work 10 and the findings of others 11 have indicated that the change in counts throughout the cardiac cycle at a particular myocardial location is proportional to the change in myocardial thickness. Thus, it should be feasible to implement a simple count-based method for quantifying myocardial thickening.

With respect to our filter selection, dynamic filters such as the image-dependent Metz¹² (or King-Metz), which offer the advantage of automatically adjusting filter parameters depending on both the count variations in the data and the object imaged, were not evaluated. It has been our clinical experience that counting statistics are fairly constant from patient to patient in Tc-99m sestamibi studies. We feel this is in part due to our acquisition protocol, which varies the dose according to the patient's weight. Since only minimal variations of counts occur in the Tc-99m sestamibi studies it was decided that the dynamic filters would offer little improvement in contrast and uniformity measurements over the values we have currently obtained using the Butterworth filter. Finally, although the performance of the dynamic filters may be an advantage in those studies that do vary in counts, the processing time required by these filters is excessive on current hardware configurations and is thus a major dis-

A new method for extracting 3-dimensional myocardial count distribution has been developed. This technique uses spherical coordinates to sample the apical region and cylindrical coordinates to sample the rest of the myocardium. Such a hybrid approach ensures a radial sampling that is mostly perpendicular to the myocardial wall, thus providing a more accurate representation of the perfusion distribution. The count distributions extracted using this technique are statistically compared with database normal limits to quantify the presence, location and extent of myocardial perfusion defects.^{2.3}

New methods for visualizing the myocardial distribution in multiple dimensions also have been developed. The methods represent the myocardial distribution in 2-dimensional polar maps and in 3-dimensional and 4-dimensional displays. The 3-dimensional rendering of myocardial distribution has the advantage of accurately representing the extent and location of perfusion defects over the distorted configuration of polar maps. Nevertheless, 2-dimensional polar maps are the de facto standards in

the field for representing myocardial perfusion distribution due to their simplicity in generation and interpretation and in the way they represent the 3-dimensional information on a single photograph.

Distance-weighted and volume-weighted polar maps have been developed to accurately represent defect location and defect extent, since no one type of polar map can accurately represent both variables due to the warped nature of these 2-dimensional mappings. We believe that combinations of these different types of visual representations should be available to diagnosticians for study interpretation.

The protocols established and the methods developed for acquiring data, quantifying and visualizing myocardial Tc-99m sestamibi distributions should provide improved image quality compared to current Tl-201 imaging as well as to Tc-99m sestamibi studies reported to date that were based on these Tl-201 protocols. Further improvements are possible by taking advantage of the monoenergetic Tc-99m spectrum and by modifying already available methodology, according to the protocols proposed, for correcting for Compton scatter and photon attenuation. The ultimate test of the value of the protocols and methods proposed will depend on how much they improve the accuracy of and confidence in the clinical interpretation of myocardial perfusion images.

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Detection and Location of Myocardial Infarction Using Technetium-99m Sestamibi Imaging at Rest

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Technetium-99m (Tc-99m) sestamibi imaging at rest has been used to detect and localize myocardial infarction. The largest study to date is a cooperative study of 146 patients in 17 institutions. There were 24 normal subjects and 122 patients with documented myocardial infarction based on clinical, enzymatic or electrocardiographic criteria. The presence of segmental myocardial perfusion defects was compared to the presence of a Q wave on the electrocardiogram or wall motion abnormality on gated blood pool scans, performed within 48 hours of the Tc-99m sestamibi study.

Of the 122 infarct patients, 148 (97%) showed perfusion abnormalities by Tc-99m sestamibi imaging. A perfusion defect was found in 110 (99%) of 111 patients with a Q wave and a wall motion abnormality, 113 (99%) of 114 patients with a wall motion abnormality and 113 (98%) of 115 patients with a Q wave. Of the 24 normal subjects, 22 (92%) had normal Tc-99m sestamibi images.

In 75% of 1,986 segments, both a Tc-99m sestamibi defect and a regional wall motion abnormality on gated blood scans were present. In 11% of segments, wall motion was normal but Tc-99m sestamibi imaging was abnormal; in 14% of segments, wall motion was abnormal and Tc-99m sestamibi images were normal. In the 24 control subjects. 99% of the segments were normal.

Thirty-eight patients had coronary angiography. A close relation existed between the coronary anatomy and myocardial Tc-99m sestamibi uptake. All 9 territories supplied by an occluded vessel and poor collaterals had grade 0 uptake (scale 0 to 2: 0 = markedly reduced; 2 = normal). Among totally occluded vessels with good collaterals, 73% had reduced uptake and 27% had normal uptake.

In 26 of these patients, the Tc-99m sestamibi uptake was compared to regional wall motion. Overall, wall motion correlated with Tc-99m sestamibi uptake. Abnormal wall motion occurred in 74% of territories with perfusion grade 0, 61% of those with grade 1 uptake and 30% of those scored as grade 2. However, 26% of territories with grade 0 uptake had normal wall motion. Furthermore, of 43 territories with reduced Tc-99m

sestamibi uptake, 12 had improved uptake after coronary bypass surgery.

These data suggest that resting Tc-99m sestamibi imaging in humans is a reliable means of detecting and localizing myocardial infarction. As a rule, uptake of Tc-99m sestamibi indicates myocardial viability, whereas reduced uptake occurs in nonviable regions. However, some regions of reduced resting Tc-99m sestamibi uptake may consist of viable but abnormally perfused myocardium.

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vocardial perfusion imaging at rest with thallium-201 (Tl-201) has been used to detect and Localize myocardial infarction. 1-8 However, there are distinct physical and physiologic disadvantages of Tl-201 for imaging at rest. It has low-energy photon emissions and a relatively long half-life. Imaging must be performed shortly after injection because of the phenomenon of redistribution, which can also occur at rest.

The development of technetium-99m (Tc-99m) sestamibi for myocardial perfusion offers the potential of overcoming these limitations. 9-14 Although this agent has been shown in experimental models to distribute in proportion to coronary blood flow, the experience in humans for the assessment of myocardial infarction is limited. This review analyzes data in humans that support its use as a perfusion agent for the assessment of myocardial infarction.

MULTICENTER TRIAL

After completing phase I and II testing of Tc-99m sestamibi, Du Pont sponsored a multicenter phase III clinical trial of the efficacy of this agent in the localization and detection of myocardial infarction. This involved 17 institutions in the United States and Canada. The diagnosis of myocardial infarction was made on clinical grounds, based on appropriate history and electrocardiographic or enzymatic documentation of a myocardial infarction, or both. Of 122 patients enrolled in the study, 50 had "acute" infarctions (imaging was performed within 14 days of the event), 61 had "previous" infarctions and 11 had both. There were 96 men and 26 women, aged 23 to 93 years. These patients were compared to 24 clinically normal subjects-9 men and 15 women, aged 25 to 55 years.15

Imaging was performed after injection of the radiopharmaceutical at rest. The injection was prepared by adding sodium-Tc-99m-pertechnetate to a commercial

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sestamibi kit (Du Pont Imaging Agent Division). The mixture was then gently agitated and boiled for 10 minutes. This produced labeling efficiency in excess of 90% in all cases. The agent was used within 6 hours of preparation. After waiting at least 1 hour after injection, we obtained planar static images for 6 to 10 minutes in 3 standard projections: anterior, best septal left anterior oblique and left lateral. All images were sent to a core laboratory at Yale New Haven Hospital for blinded analysis. Images were analyzed after dividing each of 3 projections into 5 segments for a total of 15 left ventricular segments/patient.

Although patients were entered on the basis of a clinical diagnosis of myocardial infarction, it was felt necessary to base further analysis on more objective markers of infarction. The 2 parameters chosen were the presence and location of Q waves on the electrocardiogram and the presence and location of wall motion abnormalities on rest gated cardiac blood pool scan, performed within 48 hours of the rest perfusion study with Tc 99m sestamibi. The criteria are not perfect but represented widely available objective methods of assessing the presence of myocardial infarction. The interpretation of the electrocardiogram and of the gated blood pool scans was performed at the multiple centers and compared to the core laboratory blinded readings of the Tc-99m sestamibi images. The gated scans were obtained in the same 3 projections used for Tc-99m sestamibi imaging. Wall motion was analyzed in 5 segments/view to correspond to the Tc-99m sestamibi images.

Of the 122 patients, 115 had Q waves on the electrocardiogram, and 113 (98%) of these individuals had an abnormal Tc-99m sestamibi study. Two patients without Q waves had normal Tc-99m sestamibi imaging. Therefore, there was concordance with the presence of electrocardiographic Q waves in 115 (94%) of 122 patients. With respect to wall motion patterns on gated blood pool scans, of the 98 patients with ≥1 region of akinesis or dyskinesis, 97 (99%) had a perfusion defect on the Tc-99m sestamibi images. A perfusion defect was also found in all 16 patients with hypokinesis only. Three patients with normal wall motion had normal Tc-99m sestamibi images. Therefore, there was concordance with wall motion in 116 (95%) of 122 patients. In contrast, Tc-99m sestamibi images were normal in 22 (92%) of 24 control subjects with normal electrocardiograms and gated blood pool scans.

The gated blood pool scan also permitted a segment-by-segment comparison in the 122 patients with myocardial infarction. A perfusion defect was noted in 210 (19%) of 1,122 segments with normal wall motion, 248 (58%) of 428 segments with hypokinesis and in 330 (76%) of 436 segments with akinesis or dyskinesis. Overall, there was a 75% concordance on a segmental basis, with 11% of segments having a perfusion defect with normal wall motion and 14% of segments having normal perfusion with abnormal wall motion. In the 24 normal subjects, 99% of the segments were interpreted as normal.

These data from 17 institutions demonstrate that rest Tc-99m sestamibi imaging can detect and localize infarction with a high degree of sensitivity and specificity.

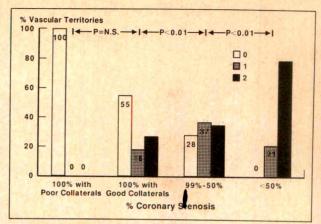


FIGURE 1. Qualitative rest left ventricular technetium-99m sestamibi uptake score (0 to 2) subgrouped on the basis of percent coronary stenosis. ¹³ The p values compare the distribution of vascular territories in different technetium-99m sestamibi uptake groups to the adjacent group. NS = not significant.

CORRELATION WITH THE PRESENCE OF CORONARY OCCLUSION

To assess whether Tc-99m sestamibi imaging could be quantified and whether it could correlate with the presence of a coronary occlusion, Dilsizian and co-workers¹³ compared the scans in 38 infarction patients with known coronary anatomy. The left ventricle was divided into 3 vascular territories corresponding to the left anterior descending, posterior descending and circumflex territories. The left ventricular uptake of Tc-99m sestamibi was quantified in 10 or 11 sectors/view and expressed in relation to the pixel with maximal counts in the left ventricular circumferential profile.

There were 31 total coronary artery occlusions in the 38 patients. Nine of these arteries had poor collaterals, all of which had markedly diminished uptake of Tc-99m sestamibi (42 ± 21%, mean ± standard deviation) by quantitative analysis. None had normal uptake (Fig. 1). The remaining 22 occlusions had good collateral flow, and Tc-99m sestamibi uptake in these territories was categorized as normal in only 27%. The mean Tc-99m sestamibi uptake in the territories of occluded arteries with good collaterals was 61 ± 23%, compared with 87 ± 10% in territories with normal vessels or stenoses <50% (p < 0.001) (Fig. 2). The results in the normal vessels suggest that 67% be used as a lower limit of normal uptake (mean - 2 standard deviations). Based on this value, quantitative analysis correctly assigned 8 of the 9 territories with poor collateral flow and occlusion and 31 of 34 regions with <50% stenosis.

These data demonstrated that with both qualitative and quantitative analysis of resting Tc-99m sestamibi images, regions with total occlusion of the coronary arteries with poor collateral flow and most regions with total occlusion and good collateral flow were detected. These results support the use of this agent for the detection and localization of coronary occlusion, which is the underlying anatomic basis for myocardial infarction.

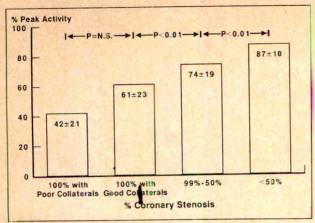


FIGURE 2. Mean distribution of the lowest quantitative rest technetium-99m sestamibi uptake in each vascular territory (expressed as a percent of peak activity) subgrouped on the basis of percent coronary stenosis. NS = not significant. (Reproduced by permission of the American College of Cardiology.13)

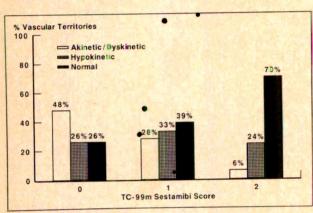


FIGURE 3. Qualitative technetium-99m (Tc-99m) sestamibi uptake in relation to regional wall motion by gated blood pool scan.14

TABLE I Quantitative Technetium-99m Sestamibi Uptake in Relation to Regional Wall Motion

	Normal/ Hypokinetic (%)	Akinetic/ Dyskinetic (%)
Regional uptake (% peak activity)*		
Grade 1 (≥50%)	77	23
Grade 2 (<50%)	9	91

CORRELATION WITH MARKERS OF POTENTIAL VIABILITY

Although the aforementioned study suggests that this perfusion agent will permit detection of coronary occlusions at rest, its relation to markers of potential viability in patients with coronary artery disease (CAD) is less clear. Recently, Rocco and co-workers14 compared Tc-99m sestamibi uptake on a regional basis to left ventricular wall motion in 26 patients. Within the limitation of

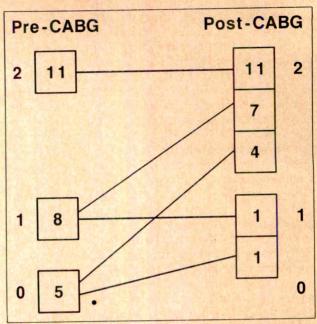


FIGURE 4. Qualitative technetium-99m sestamibi perfusion grading in 24 vascular territories before and after coronary artery bypass grafting (CABG) for the 8 patients who underwent surgical revascularization. (Reproduced by permission of the American College of Cardiology. 14)

comparing perfusion to function on separate imaging studies, the investigators demonstrated that 14 (52%) of 27 territories with markedly reduced Tc-99m sestamibi uptake by qualitative analysis had some retained wall motion, and that in half (26%) of these territories, wall motion was normal (Fig. 3). This suggested that some regions with reduced perfusion at rest can have viability as evidenced by retained contraction. Of the 14 territories with reduced uptake and normal motion or hypokinesis, only 1 (7%) was associated with an occluded artery with poor collateral flow. In contrast, 8 (62%) of 13 zones associated with akinesis or dyskinesis on the corresponding gated cardiac blood pool scan had occluded arteries with poor collateral flow.

In these 27 territories, quantitative analysis improved the discrimination between retained versus absent wall motion. Mean Tc-99m sestamibi uptake in the 14 territories with retained motion was 62 ± 15%. Expressed another way, wall motion was retained in 77% of regions showing ≥50% of maximal uptake of Tc-99m sestamibi. Absent motion in 13 territories was associated with a mean Tc-99m sestamibi uptake of $39 \pm 16\%$ (p = 0.02), with 91% of these regions having <50% uptake (Table I). Therefore, reduced uptake of a less intense nature is usually associated with viability, but when the uptake decreases below 50% in a zone, viability is less common. The amount of Tc-99m sestamibi uptake thus appears to be a correlate of potential myocardial viability.

The value of this 50% cutoff for viability was supported by a limited study in 8 patients scanned before and after coronary artery bypass grafting (CABG). Improvement in Tc-99m sestamibi uptake after CABG was presumed to be a marker of myocardial viability. One would not expect any tracer retention in myocardial scar despite successful revascularization. Tc-99m sestamibi uptake improved after revascularization in 11 (61%) of 18 segments with markedly reduced uptake preoperatively. Of the segments with abnormal uptake (50 to <67%) preoperatively, 80% improved after revascularization. In contrast, only 39% of regions with initial uptake of Tc-99m sestamibi below 50% of maximum showed significant improvement after revascularization (Fig. 4). Once again, moderate reduction of Tc-99m sestamibi uptake implies a greater likelihood of potential viability than when the perfusion abnormality is severe.

This study showed that resting myocardial perfusion can be reduced to a moderate degree while contractile function is maintained, indicating a dissociation between perfusion and function. With more severe degrees of underperfusion, retained contraction (and hence myocardial viability) is less likely. Unfortunately, retained wall motion and improvement in uptake after coronary bypass surgery are not perfect markers of viability. The data suggest that in its role as a perfusion agent, Tc-99m sestamibi may also be used to evaluate viability by the severity of the underperfusion.

CONCLUSION

Tc-99m sestamibi imaging at rest is a useful method for assessing regional perfusion and is of value in the detection of myocardial infarction. The perfusion abnormality can be readily localized and easily imaged, taking advantage of the improved physical properties of Tc-99m in comparison with Tl-201. In the setting of acute myocardial infarction, this approach is likely to be an excellent method of quantifying noninvasively the severity and location of the infarction, and of demonstrating whether thrombolytic therapy has improved perfusion. ^{16,17} Tc-99m sestamibi is less likely to play a major role in initial detection of acute infarction. However, if in such cases the early Tc-99m sestamibi study is normal, early discharge from the emergency room or coronary care unit may be justified.

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Thrombolytic Therapy for Myocardial Infarction: Assessment of Efficacy by Myocardial Perfusion Imaging with Technetium-99m Sestamibi

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Technetium-99m (Tc-99m) sestamibi has been used to evaluate the afficacy of thrombolytic therapy. Improved image quality due to the higher photon energy of Tc-99m and the increased allowable doses of this radiopharmaceutical along with its lack of redistribution makes Tc-99nf sestamibi an acceptable imaging agent for such studies. This imaging agent was used for serial quantitative planar and tomographic imaging to assess the initial risk area of infarction, its change over time and the relation to infarct-related artery patency in patients with a first acute myocardial infarction. Twentythree of 30 patients were treated with recombinant tissue-type plasminogen activator (rt-PA) within 4 hours after onset of acute chest pain. Seven patients were treated in the conventional manner and did not receive thrombolytic therapy. The initial area at risk varied greatly both in patients treated with rt-PA and in those who received conventional therapy, Patients with successful thrombolysis and patent infarct arteries had a significantly greater reduction of Tc-99m sestamibi defect size than patients who had persistent coronary occlusion. Serial imaging with Tc-99m sestamibi could find important application in future clinical research evaluating the efficacy of new thrombolytic agents. Direct measurements of the amount of hypoperfused myocardium before and after thrombolysis could provide rapid and unequivocal results using fewer patients and avoiding the use of "mortality" as an end point. This approach has not yet been widely tested in the clinical arena.

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hrombolytic therapy has been shown convincingly in numerous clinical trials to reduce mortality after acute myocardial infarction. 1-12 A recent report indicates that this initial favorable effect is sustained over a 5-year period. 13 The ultimate aim of thrombolytic therapy in acute myocardial infarction is to restore blood flow to the risk area and thus limit the area of necrosis and salvage viable myocardium. In the prethrombolytic era a definite relation was demonstrated between global left ventricular ejection fraction (LVEF) at hospital discharge and subsequent 1-year survival.14 Accordingly it was expected that the observed improvement in survival after thrombolytic therapy would be reflected in significant preservation of global left ventricular function. However, in most trials LVEF was only marginally better in patients who received thrombolytic therapy, compared to those who received placebo treatment. 6,7,15-19 Therefore the marked improvement in survival could not be fully explained by preservation of cardiac pump function. Nevertheless, in clinical practice significant improvement of LVEF has been observed after thrombolytic therapy in individual patients.

Previously we demonstrated considerable spontaneous variability in LVEF in patients with acute myocardial infarction.²⁰ We propose that this observation may provide a potential explanation for the overall somewhat disappointing effect of thrombolytic treatment on mean LVEF in large groups of patients. Significant improvement of LVEF in individual patients with successful thrombolysis may be masked and blunted when LVEF is expressed as a mean value. In addition, there may be the paradox of low LVEF in patients who survived because of thrombolytic therapy, but otherwise would have died.

Furthermore, improvement of LVEF may be delayed by the effect of "myocardial stunning" after severe ischemic injury.²¹ On the other hand, the effect of improvement of regional function within the infarct areas on global LVEF may be masked by a decrease of hyperkinesis in noninfarct zones.²² Remodeling of the infarct area could also affect measurement of LVEF.²³ Finally, LVEF is significantly dependent on ventricular loading conditions. These may change at various times after acute infarction.

For these reasons LVEF would appear not to be a most appropriate parameter for assessing the effect of thrombolytic therapy.

MYOCARDIAL PERFUSION

If left ventricular function improves after successful thrombolysis, this is secondary to improvement of myo-

cardial blood flow through the infarct artery. Improvement of myocardial perfusion after thrombolysis has been demonstrated by several investigators using serial thallium-201 (Tl-201) imaging.²⁴⁻²⁶ Unfortunately, serial imaging with Tl-201 is not practical in the setting of thrombolytic therapy. To visualize the extent of hypoperfused myocardium before thrombolytic treatment, initiation of therapy would have to be delayed for at least 30 minutes. Obviously, since time is of the essence for salvaging myocardium, such an imaging protocol is clinically unacceptable. Technetium-99m (Tc-99m) sestamibi has definite advantages over Tl-201 in the setting of thrombolytic therapy for acute infarction. 27-29 This Tc-99m-labeled imaging agent accumulates in the heart proportional to the distribution of regional myocardial blood flow, similar to Tl-201.30,31 However, unlike Tl-201 no significant redistribution occurs. 32-35 Therefore, Tc-99m sestamibi images "freeze" the pattern of myocardial perfusion at the moment of injection for a prolonged period of time. Another important advantage is a 10 times larger dose of radiopharmaceutical that can be administered. This results in considerably better image quality than with Tl-201 36

We used these characteristics of Tc-99m sestamibi to evaluate the efficacy of thrombolytic therapy in patients with acute myocardial infarction. ^{37–39}

IMAGING PROTOCOL

In a multicenter trial involving Yale University School of Medicine (New Haven, Connecticut), Mayo Clinic (Rochester, Minnesota) and Baylor College of Medicine (Houston, Texas), patients were imaged using the protocol outlined in Figure 1. Patients with a first acute myocardial infarct received 20 to 25 mCi of Tc-99m sestamibi intravenously before, or at the initiation of, thrombolytic therapy. Myocardial perfusion images were acquired as soon as the patient was clinically stable. In this pilot study 30 patients had planar imaging, of whom 16 also had tomographic imaging. Twenty-three patients received thrombolytic therapy and 7 patients received conventional treatment for their infarction. The first myocardial perfusion images were assumed to demonstrate the area at risk. Subsequently, the patients had a second study 18 to 48 hours later, and a third study at the time of hospital discharge. The extent of perfusion defects on the second or third study, or both, was assumed to demonstrate the ultimate size of infarction. A decrease in size of the perfusion defect on the second or third study in comparison to that on the first study was assumed to represent the extent of myocardial salvage.

In a subgroup of patients the pattern of myocardial perfusion on serial Tc-99m sestamibi imaging was correlated with delayed accumulation of Tl-201 after submaximal exercise performed at hospital discharge. The distribution of Tl-201 on delayed (2 to 3 hours) images was assumed to provide an approximation of the extent of viable myocardium.

The size of myocardial perfusion defects was quantified for both planar and tomographic studies using previously validated methodology. 38-40

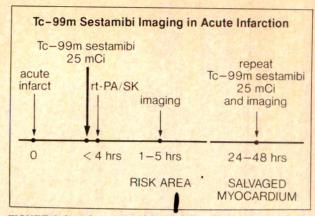


FIGURE 1. Imaging protocol for serial imaging before and after thrombolytic treatment with intravenous recombinant tissue plasminogen activator (rt-PA) or streptokinase (SK). Tc-99m = technetium-99m.

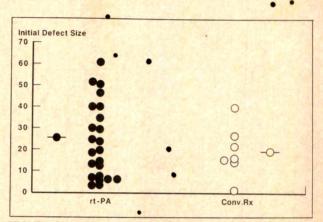


FIGURE 2. Initial risk zone size in 23 patients treated with recombinant tissue plasminogen activator (rt-PA) and 7 patients treated conventionally (Conv. Rx). (Reproduced with permission of the American College of Cardiology.³⁸)

SERIAL IMAGING IN THROMBOLYSIS

Patients with acute myocardial infarction, regardless of whether treated with a thrombolytic agent, showed marked variation in size of the area at risk (Fig. 2). This could not be predicted from either the clinical presentation in the emergency room, the location of infarction or the site of occlusion of the infarct artery on coronary angiography (i.e., proximal or distal in the vessel).

Twenty of 30 patients had a smaller total myocardial perfusion defect size on the second study (Fig. 3). The relative change in the amount of hypoperfused myocardium over time was variable in both patients who received thrombolytic therapy, and patients who received conventional therapy (Fig. 4). Patients with an open infarct artery had a significantly larger decrease in defect size than patients with an occluded infarct artery. All patients who had a decrease in defect size >30% on planar imaging had open infarct arteries. Similar observations were made by tomographic imaging.³⁹

It is of interest that in approximately 50% of the patients the decrease in defect size continued or occurred relatively late after thrombolytic therapy (Fig. 5). The

THROMBOLYSIS

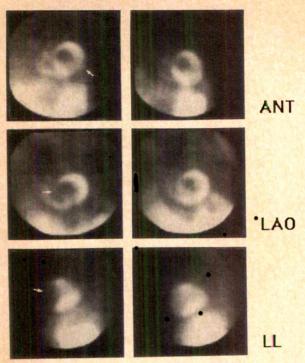


FIGURE 3. Serial planar technetium-99m sestamibi imaging before and after thrombolysis. The images are of a patient with an acute anteroseptal myocardial infarction. This patient had successful thrombolysis of the left anterior descending artery. An anteroseptal myocardial perfusion defect is present (arrows). Quantitative analysis revealed a 33% change in defect size. Improved uptake of technetium-99m sestamibi can be appreciated in the septum, and anterior wall. ANT = anterior view; LAO = left anterior oblique view; LL = left lateral view.

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pathophysiologic mechanisms for this observation are at present not clear. These could include no-reflow to the infarct region, delayed recovery of coronary flow reserve, delayed recovery of metabolic function, geometric changes of the left ventricle, or a combination of these factors.

There was no significant correlation between the change in myocardial perfusion (i.e., a true visualization of the effect of reperfusion) and 1 single measurement of LVEF at hospital discharge (Fig. 6). This is of note since LVEF has been used in numerous clinical trials to evaluate the efficacy of thrombolytic treatment. In contrast, as could be expected, there was a good correlation between LVEF and the size of planar/tomographic Tc-99m sestamibi defects on the study performed closest to the ejection fraction evaluation (Fig. 7).

IMPROVED PERFUSION ON SERIAL IMAGING AND DELAYED THALLIUM-201 UPTAKE

Although improved uptake of Tc-99m sestamibi correlated with reperfusion of the infarct-related artery, this does not necessarily imply preservation of viable myocardium. ^{41–45} Reperfusion could have occurred too late to salvage myocardium. Despite the well-recognized limita-

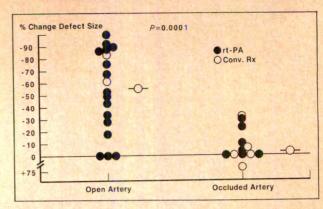


FIGURE 4. Change in size of myocardial perfusion defect and status of the infarct artery. Abbreviations as in Figure 2 (reproduced with permission of the American College of Cardiology).³⁸

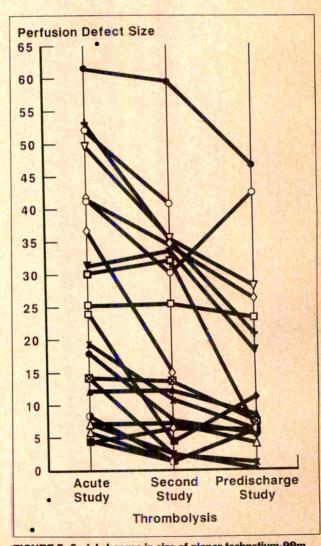


FIGURE 5. Serial changes in size of planar technetium-99m sestamibi perfusion defects after thrombolytic therapy. Defect size was assessed before thrombolysis (acute study, n = 23), 18 to 48 hours after thrombolysis (second study) and at hospital discharge (n = 17). Compared to the acute study, 16 of 23 patients had smaller defects on the second study. Subsequently 10 of 17 patients had a further decrease in defect size on the hospital discharge study. The symbols indicate individual patients.

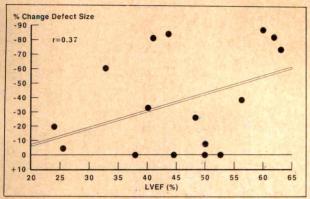


FIGURE 6. Lack of correlation between change in technetium-99m sestamibi perfusion defect size and left ventricular ejection fraction (LVEF) at hospital discharge.

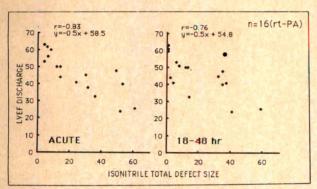


FIGURE 7. Correlation between global left ventricular ejection fraction (LVEF) at hospital discharge and total technetium-99m sestamibi defect size on the early (acute) study (before thrombolysis) and on the 18 to 48 hour study (after thrombolysis). (Reproduced with permission of the American College of Cardiology.³⁸)

tions of delayed Tl-201 imaging to identify viable myocardium after exercise in all instances, normal Tl-201 uptake at delayed imaging indicates with reasonable certainty myocardial viability. 46-48 In the subgroup of patients who had quantitative Tl-201 exercise imaging at hospital discharge, an overall good agreement existed between the uptake of both radiopharmaceuticals. Importantly, there was no systematically greater uptake of Tc-99m sestamibi compared to Tl-201. Thus, improved uptake of Tc-99m sestamibi on serial imaging after thrombolytic therapy appears not only to indicate reperfusion of the infarct-related artery, but also salvage of viable myocardium.

CLINICAL IMPLICATIONS

These initial observations indicate that quantitative serial imaging with Tc-99m sestamibi provides a means to categorize patients with acute myocardial infarction who undergo thrombolytic therapy. These patients now can be defined according to the initial risk area, the extent of myocardial reperfusion and extent of myocardial salvage. Our preliminary results have been confirmed by other investigators in experimental and clinical studies. Furthermore it has been demonstrated that reduction in defect size was predictive of late improvement of echocardiographic regional wall motion.

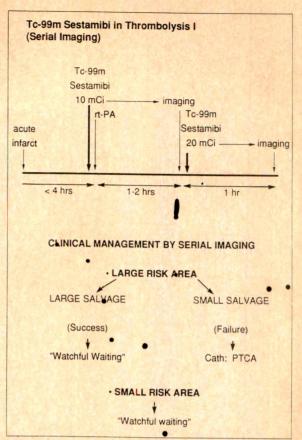


FIGURE 8. Proposed clinical management of patients using serial imaging with Tc-99m sestamibi, before and after thrombolytic therapy. Cath = catheterization; PTCA = percutaneous transluminal coronary angioplasty; other abbreviations as in Figure 1.

Based on these preliminary results, it appears that serial imaging with Tc-99m sestamibi may find important application in future clinical research and trials, evaluating the efficacy of new thrombolytic agents. Rather than using mortality (which requires a larger number of patients) or LVEF (which may be blunted for the aforementioned reasons) as study end points, direct measurement of the amount of hypoperfused myocardium before and after thrombolysis could provide rapid and unequivocal results in trials with fewer patients.

Applicability to clinical practice: We propose that serial imaging with Tc-99m sestamibi would permit better selection of patients who may benefit from more aggressive treatment after thrombolytic therapy. The results of the Thrombolysis in Myocardial Infarction Phase II Trial have shown that indiscriminate application of an "Invasive Strategy" (i.e., coronary angiography and percutaneous transluminal coronary angioplasty) has no advantage compared with the "Conservative Strategy" (i.e., "watchful waiting" and percutaneous transluminal coronary angioplasty performed only in patients with clinical evidence of recurrence of myocardial ischemia). 45

Figure 8 illustrates how serial Tc-99m sestamibi imaging could be used to identify high- and low-risk patients and to choose subsequent clinical management. One can imagine 2 extreme situations after serial Tc-99m imag-

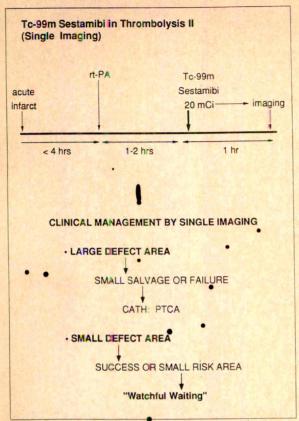


FIGURE 9. Proposed clinical management of patients on the basis of results of a single Tc-99m sestamibi image after thrombolytic therapy. Abbreviations as in Figures 1 and 8.

ing: (1) A patient may have a large myocardial area at risk and no, or only small, area of apparent salvage. Such a patient one could consider to be a failure of thrombolytic therapy and at high risk. In this situation we would propose that the aggressive invasive strategy is justified. (2) A patient may have either a large area of myocardial salvage as the result of successful thrombolysis, or the patient may have only a small myocardial area at risk (with or without substantial salvage). The latter patient one could consider to be at low risk. A more conservative approach and watchful waiting would be defensible.

Single injection protocol: In the present protocol Tc-99m sestamibi was injected before and after thrombolytic therapy. In daily clinical practice it may be difficult to have the radiopharmaceutical prepared on a few minutes notice for immediate use in emergency room. This would obviously limit the practical usefulness of Tc-99m sestamibi to evaluate the efficacy of thrombolytic therapy. However, it is conceivable that meaningful clinical decisions can be made by 1 single injection after thrombolytic treatment. In Figure 9 we propose a potential algorithm for management of patients after thrombolysis on the basis of a single set of myocardial perfusion images. A similar reasoning, as outlined for serial imaging, could direct management of patients. Patients with large defects could be considered failures of thrombolytic treatment. Either no reperfusion occurred or the extent of myocardial salvage is minimal. These patients could be considered candidates for the aggressive invasive strategy. On the other hand, patients with small defects either had successful thrombolysis or had only a small initial risk area. In either case, such patients could be considered to be at low risk. The conservative approach of watchful waiting for clinical evidence of ischemia would appear to be justified in the latter patients.

It should be emphasized that these approaches have yet to be tested in the clinical arena. However, it is conceivable that serial quantitative imaging with Tc-99m sestamibi could place the important results of the Thrombolysis in Myocardial Infarction Phase II Trial⁵² in practical clinical perspective.

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Detection and Assessment of Unstable Angina Using Myocardial Perfusion Imaging: Comparison Between Technetium-99m Sestamibi **SPECT and 12-Lead Electrocardiogram**

Jean Grégoire, MD, and Pierre Théroux, MD

Forty-five studies using technetium-99m (Tc-99m) sestamibi single photon emission computed tomography (SPECT) were performed on patients hospitalized for spontaneous chest pain suggestive of myocardial ischemia. The studies were done after an injection during an episode of chest pain and a repeated injection when the patients were free of pain. All patients were hospitalized with a presumed diagnosis of unstable angina, and none had evidence of a previous myocardial infarction. The presence of a perfusion defect observed with Tc-99m sestamibi injected during chest pain had a 96% sensitivity and a 79% specificity for the detection of significant coronary artery disease (stenosis ≥50%) on subsequent angiography. When the criterion of a larger perfusion defect during pain compared to absence of pain was used, the sensitivity was 81% and the specificity was 84%. In contrast, transient electrocardiographic ischemic changes during pain had a sensitivity of 35% and a specificity of 68%; electrocardiographic changes during or outside episodes of chest pain had a sensitivity of 65% and a specificity of 63% for the diagnosis.

Tc-99m sestamibi SPECT represents a reliable noninvasive diagnostic tool that could aid in the diagnosis of myocardial ischemia in patients with spontaneous chest pain and provide additional information to that provided by the electrocardiogram.

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noninvasive test that could accurately identify myocardial ischemia in patients with spontane-Lous chest pain would be extremely useful to aid diagnosis, orient investigative procedures and guide treatment in patients with suspected unstable angina.

Both imaging agents currently available—thallium-201 (Tl-201) and technetium-99m (Tc-99m) sestamibi—have a rapid myocardial uptake proportional to blood flow even in conditions of low coronary blood flow.^{1,2} Tc-99m sestamibi possesses the advantage of minimal redistribution. The ratio of uptake between ischemic and normal myocardial areas is determined within minutes after injection and remains constant for hours.1 Tc-99m sestamibi can thus be injected at a selected time and scintigraphic acquisition performed 6 to 8 hours later, preventing any delay in the initiation of treatment.

In contrast, Tl-201 redistribution begins a few minutes after injection. This phenomenon is characterized by the passage of Tl-201 back and forth between the intracellular and the extracellular space until an equilibrium is reached. The time required to reach equilibrium depends on the coronary blood flow and is longer with more severe reduction in blood flow. Therapy used to improve regional blood flow during an acute ischemic event can accelerate this redistribution. Scintigraphy should therefore be performed before treatment is instituted. This represents a major problem for patients who have acute coronary artery syndromes in whom spontaneous chest pain can occur at any time, when emergency treatment may be required immediately.

A disadvantage of Tc-99m sestamibi is that redistribution images, which are obtained 3 to 4 hours or 24 hours after the injection when using Tl-201, are not possible. Assessment of myocardial perfusion during the basal state thus requires a second injection of Tc-99m sestamibi. Tc-99m sestamibi also demonstrates high liver extraction, which may interfere with visualization of the inferior wall of the heart. This problem can be circumvented by ingestion of a light meal after the injection of Tc-99m sestamibi and by delaying image acquisition for at least 1 hour after the injection.

The physical properties of Tc-99m sestamibi are superior to those of Tl-201. Its gamma ray emission is optimal for current cameras, and permits better dosimetry, higher doses and consequently better photon flux. First-pass studies³ and gated acquisitions⁴ can be obtained. Tc-99m sestamibi importantly is also readily available as a kit preparation. In addition, since Tc-99m sestamibi demonstrates minimal redistribution, single photon emission computed tomography (SPECT) imaging can be used to delineate zones of hypoperfusion in patients with acute coronary syndromes without the requirement for rapid imaging associated with thallium-201.

For these various reasons, Tc-99m sestamibi may actually represent the best imaging agent for the investigation of acute coronary syndromes. Previous studies at our institution and other centers have suggested that it could be useful to define the area at risk and the area of necrosis in acute myocardial infarction.⁵⁻⁸ We recently published a preliminary report on its potential usefulness in unstable angina.⁹ The goal of the present study was to evaluate the diagnostic value of Tc-99m sestamibi in patients with spontaneous chest pain hospitalized with a presumed diagnosis of unstable angina. Its sensitivity and specificity was compared to that of 12-lead electrocardiography.

METHODS

All patients with spontaneous chest pain suggestive of myocardial ischemia were considered for the study. Exclusion criteria consisted of acute myocardial infarction determined by a doubling of the creatine kinase enzymes with presence of the MB fraction or the appearance of a new Q wave, a previous well-documented myocardial infarction or a contraindication to coronary angiography. Forty-five studies performed on 43 patients (24 men, 19 women, mean age: 58 years) were included in the analysis. Tc-99m sestamibi (1 GBq [27 mCi]) was injected during an episode of spontaneous chest pain while a 12-lead electrocardiogram was obtained.

Radioisotopic diagnosis: SPECT acquisition was performed 1 to 6 hours after the Tc-99m sestamibi injection. A rotating large-field-of-view SPECT camera equipped with a low-energy, high-resolution, parallel-hole collimator was used for image acquisition. Sixty-four projections of 20 to 30 seconds each were obtained over a 360° variable elliptical orbit on a 64 × 64 × 16 byte matrix with a zoom of 1.44. A 20% symmetric energy window centered on the 140 keV peak was used. Processing was done using filtered back-projection with a Butterworth filter (cutoff: 0.7, order: 8) without attenuation correction. Orthogonal tomographic slices, each 1 pixel thick (6.4 mm), were reconstructed parallel to the vertical and horizontal long axes and the short axis of the left ventricle. Using the short-axis slices, a 2-dimensional polar map display was constructed.10

Twenty-five regions of interest of equal size were automatically drawn on each polar map display and the relative uptake in each of these sectors was determined and normalized to the sector with the maximal value. Values were compared to those of a file of rest Tc-99m sestamibi SPECT studies obtained from 15 normal volunteers with a probability of coronary artery disease <1%. A sector was considered abnormal when normalized counts were >2 standard deviations below the normal mean. Defect size was calculated as the ratio of the number of abnormal sectors to the total number of sectors. Defect intensity was defined as the ratio of the average normalized counts in the abnormal sectors to the corresponding normal means, subtracted from 1. A glob-

al defect score was calculated as the product of defect size and defect intensity. A study was considered abnormal when the global score was higher than 1. Patients with an abnormal study had a repeated Tc-99m sestamibi injection and acquisition 24 to 48 hours later when free of chest pain.

electrocardiogram was considered abnormal in the presence of ST-segment depression or elevation 1 mm or more in amplitude, T-wave inversion in at least 2 contiguous leads, or a combination of these. An electrocardiogram was repeated at the time of Tc-99m sestamibi injection during the chest pain episode. Ischemic electrocardiographic changes during the chest pain were defined as the appearance or the accentuation of the ischemic signs on the basal electrocardiogram or a pseudonormalization of previously negative T waves. All electrocardiograms were interpreted by 2 observers, blinded to the results of the scintigraphic studies.

Angiographic diagnosis: Coronary angiography was performed within 10 days of the scintigraphic studies according to previously described methods, 11 and findings were interpreted by a consensus of 2 observers. 12 Any query was solved using Coronary Artery Surgery Study quantitative analysis. 13,14 Lumen diameter reduction ≥50% was considered significant.

RESULTS

The results are summarized in Figure 1. The presence of a perfusion defect observed with Tc-99m sestamibi injected during chest pain was seen in 25 of 26 patients with significant coronary artery disease (sensitivity: 96%), and the Tc-99m sestamibi study was normal in 15 of 19 patients with no significant coronary artery disease (specificity: 79%). In this population, the positive and negative predictive values were 86 and 94%, respectively. Of the 4 false-positive cases, 2 were in patients with ST-segment elevation during chest pain, and a presumed diagnosis of vasospastic angina was made. One female patient had a small anterior defect thought to be caused by a breast artifact, and 1 patient demonstrated a small posterobasal defect.

In patients demonstrating an abnormal initial study, the repeated study while free of pain was normal in 8, showed partial improvement in 13 and was unchanged in 4. A larger perfusion defect, defined as a difference in global score >1, on the study obtained after injection during chest pain compared to the study done while free of pain, was present in 21 patients with significant coronary artery disease (sensitivity: 81%), and absent in 16 patients with no significant coronary lesion (specificity: 84%). An example of a study obtained during and after an episode of chest pain in a patient with a 70% left anterior descending artery stenosis is shown in Figure 2. An example of a false-positive result is shown in Figure 3. This patient had transient ST-segment elevation during chest pain and a clinical diagnosis of coronary artery spasm.

Transient ischemic changes observed on the electrocardiogram obtained simultaneously with the radioiso-

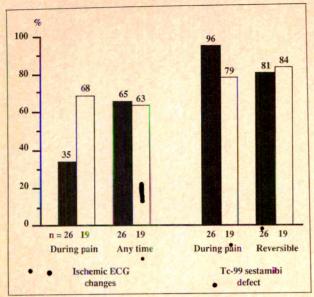


FIGURE 1. Comparison of 12-lead electrocardiography and technetium-99m (Tc-99m) sestamibi single photon emission computed tomography for the detection of significant coronary artery disease. Tc-99m sestamibi scintigraphy after injection during chest pain had the highest sensitivity for the diagnosis. It has a better accuracy than the 12-lead electrocardiogram obtained during or between episodes of chest pain. Use of the criterion of a reversible Tc-99m sestamibi defect slightly increases the specificity for the diagnosis of significant coronary disease but decreases its sensitivity. ECG = electrocardio-

tope injection at the time of chest pain showed a sensitivity of 35% (9 of 26) and a specificity of 68% (13 of 19), whereas the presence of ischemic signs on electrocardiograms obtained either during or in the absence of pain had a sensitivity of 65% (17 of 26) and a specificity of 63% (12 of 19) (Fig. 1).

DISCUSSION

In this study of patients without a previous myocardial infarction and with spontaneous chest pain presumed to represent unstable angina, a perfusion defect was objectively detected in all but 1 patient with significant coronary disease when Tc-99m sestamibi was injected during a symptomatic episode. However, a few patients without any significant coronary stenosis also showed a myocardial perfusion defect during pain.

Whereas the sensitivity can hardly be improved, a number of reasons can explain the false-positive results (Table I). Vasospastic angina and myocardial ischemia without underlying severe fixed coronary stenosis can be present in some of these patients. Small undetected myocardial infarctions after thrombus formation and spontaneous lysis can also be present in some patients. Finally, technical factors such as tomographic reconstruction artifacts, patient movement during acquisition, breast attenuation in female patients and diaphragmatic attenuation could produce false perfusion defects. Despite these potential limitations, Tc-99m sestamibi SPECT was highly sensitive and specific in this study for the diagnosis of myocardial ischemia and significant coronary artery dis-

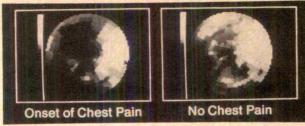


FIGURE 2. Two-dimensional polar map display of a technetium-99m sestamibi study obtained in a 48-year-old man with no known coronary disease admitted for atypical chest pain at rest. The study obtained during an episode of chest pain shows a large myocardial perfusion defect involving the anterior and septal walls. The electrocardiogram obtained at the time of the injection showed T-wave inversions in the precordial leads. The scintigraphy obtained in the absence of chest pain demonstrates almost complete recovery of the perfusion defect. A 70% proximal left anterior descending artery lesion was subsequently found at angiography.

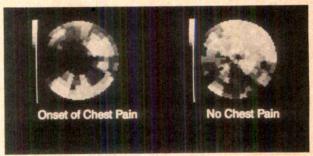


FIGURE 3. Technetium-99m sestamibi study obtained in a 55-year-old man with known coronary disease and previous successful left anterior descending coronary artery percutaneous angioplasty. The patient was admitted with the diagnosis of typical chest pain. Scintigraphic images obtained after an injection during chest pain demonstrate moderate hypoperfusion of the septal wall with lesser involvement of the anterior wall. Myocardial perfusion in the absence of chest pain is normal. Coronary angiography demonstrated an absence of restenosis. The electrocardiogram, however, documented transient ST-segment elevation in the septal leads during an episode of chest pain. The clinical diagnosis was Prinzmetal's variant angina.

TABLE I Possible Causes of Abnormal Technetium-99m Sestamibi Myocardial Uptake in the Absence of Significant Coronary Artery Disease

Coronary artery vasospasm

Previous myocardial infarction with coronary recanalization Noncoronary cardiac disease

Artifacts:

Breast or diaphragmatic attenuation

Patient movement

Tomographic reconstruction

ease, and added significant information to the 12-lead electrocardiogram.

Comparison with thallium-201 studies: Scintigraphic perfusion studies performed so far in patients with spontaneous angina have used Tl-201. Their results are summarized in Table II. 15-21 In these studies, only very

Investigators	No. Patients	% Patients with TI-201 Perfusion Defects	Comments
TI-201 injection during ches	st pain	Alta control	
Maseri et al ¹⁵	6	100	Patients with Prinzmetal's variant angina and ST-segment elevation
Parodi et al ¹⁶	21	90	Rest angina with ST-segment depression or pseudonormalization of T wave during pain
TI-201 injection between ep	isodes of chest pain		position of the defining paint
Wackers et al ¹⁷	98	39	Perfusion defect was predictive of complicated course
Gewirtz et al ¹⁸	20	75	Perfusion defects reversible in 58% of patients
Berger et al ¹⁹	14	53	Perfusion defects corresponding to most severe coronary artery lesions
Freeman et al ²⁰	33	82	Includes TI-201 washout abnormalities
Brown et al ²¹	31	58	Perfusion defects more frequent in patients who also had effort angina compared to rest angina only

few patients have been studied with Tl-201 injected during episodes of chest pain. ^{15,16} These were highly selected patients with the diagnosis of Prinzmetal's variant angina. All patients also had electrocardiographic changes during episodes of ischemia. The sensitivity of Tl-201 was 100% in the 6 patients with ST-segment elevation, 86% in the 14 patients with ST-segment depression and 100% in the 7 patients with pseudonormalization of previously negative T waves. In 8 of these patients, the episode of chest pain was induced by ergonovine. In our study, the sensitivity was similar, showing that the results can be extended to a nonselected population with chest pain at rest and hospitalized for unstable angina.

Reports on unstable angina with Tl-201 injected between episodes of chest pain have involved more patients. Tl-201 perfusion defects have been detected with sensitivities between 39 and 75%, 17-21 similar to the 68% (17 of 25) sensitivity we observed when limiting the analysis to pain-free studies in patients with an abnormal scintigram after chest pain injection. The perfusion defects are usually seen in areas perfused by the most stenotic vessels, 19 and they could be more frequent in patients with exertional angina and unstable angina than in angina at rest only.21 Washout abnormalities have also been described. 20 Finally, when present, the perfusion defects can help predict prognosis; in the study by Wackers et al, 17 76% of the patients with a complicated clinical course had perfusion defects, compared to only 32% of the patients with an uncomplicated outcome.

Tl-201 uptake by the myocardial cell is a marker of myocardial viability. Although 24-hour redistribution imaging is a better predictor of viability than the traditional 3- to 4-hour study, the absence of redistribution does not imply cell death.²² Tc-99m sestamibi does not significantly redistribute, which may preclude assessment of cell viability in the presence of resting hypoperfusion. Perfusion defects are present in the majority of patients after an injection when free of pain. Different explanations can be found for these findings. As with Tl-201, postischemic cell dysfunction could affect Tc-99m sesta-

mibi extraction or retention. 2,23,24 Silent ischemia can also be present along with severe coronary obstruction caused by an atherosclerotic, thrombotic or vasospastic component in the absence of clinical symptoms.

Potential applications: The potential applications of Tc-99m sestamibi that can be derived or extrapolated from this study are summarized in Table III. The test can be used for the differential diagnosis of chest pain when other forms of provocative testing are usually contraindicated. It can locate the area of ischemia and thus indirectly help identify the culprit coronary artery lesion in patients with multivessel disease. This can help decide the best treatment and guide angioplasty when indicated. It can also be hypothesized that quantification of the hypoperfused area during chest pain may have prognostic value for the occurrence of cardiac events and, by defining an area at risk, the extent and severity of an eventual myocardial infarction. The presence and amount of hypoperfused myocardium present between episodes of chest pain may also help elucidate some of the pathophysiologic mechanisms involved in chest pain occurring at rest and evaluate the activity of the disease and the response to treatment. This information may aid in risk stratification. Some of these potential applications are currently under investigation in our laboratory.

Logistic implications: For highest sensitivity, the imaging agent must be injected during an episode of chest pain. Widespread application would thus require around-the-clock availability of Tc-99m sestamibi since the timing of occurrence of pain is unpredictable. The 6-hour

TABLE III Potential Applications

Differential diagnosis of chest pain
Selection of patients for coronary angiography
Identification of the culprit coronary artery lesion
Selection of best treatment
Evaluation of success or failure of treatment
Insight into pathophysiologic mechanisms
Risk stratification

shelf-life recommended by the manufacturer can be an important limiting factor at night or during the weekend. The shelf-life could possibly be extended to 12 hours by improving the stability of Tc-99m sestamibi. Also, an automated technique allowing rapid labeling of the product with minimal intervention and without expertise in radiopharmacy could be a solution for the future.

CONCLUSION

The results suggest that Tc-99m sestamibi could be very useful for the evaluation of patients with spontaneous chest pain and add new information to the currently available techniques of investigation. A negative study after injection during a chest pain episode appears to rule out significant coronary stenosis with a high level of confidence, whereas a positive study predicts with high accuracy the presence of significant coronary stenosis. A decrease in the size of a perfusion defect between images obtained during chest pain and while free of pain further supports the diagnosis of myocardial ischemia. Continuing research is necessary to evaluate further the potential usefulness of Tc-99m sestamibi to assess prognosis in unstable angina and the influence of therapy.

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Planar Imaging Techniques Used with Technetium-99m Sestamibi to Evaluate Chronic Myocardial Ischemia

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The results of published and some unpublished studies comparing planar imaging performed with 2 radionuclides, thallium-201 (TI-201) and technetium-99m (Tc-99m) sestamibi, are reviewed. The average sensitivity for the detection of coronary artery disease (CAD) in studies involving 594 patients was 85% (range 73 to 96%). The average sensitivity for individual vessels was 65% (range 60 to 70%). The average segmental concordance between TI-201 and Tc-99m sestamibi was 89%. End-diastolic gated perfusion images improved the concordance between Tc-99m sestamibi and angiography in 22 patients from 83.4 to 87%. Semiquantitative analysis increased the concordance between TI-201 and Tc-99m sestamibi from 89 to 91%. Ventricular function derived from gated Tc-99m sestamibi perfusion images showed a significant correlation with echocardiography (n = 62. r = 0.85); with angiography (n = 70, r = 0.91); and with equilibrium radionuclide ventriculography (n = 18, r = 0.86). The ratio of lung to left ventricle uptake and the ratio of right ventricle to left ventricle uptake was assessed. Eight of 52 patients had an abnormally elevated lung index (>42%) and these patients had the most severe CAD. Six of the 52 patients had an abnormally elevated right ventricular index (>56%) and these patients had more severe CAD.

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adionuclide myocardial perfusion imaging using planar imaging with thallium-201 (Tl-201) is a well-established clinical technique for the diagnosis and assessment of patients with coronary artery disease (CAD). Although Tl-201 is the most widely used perfusion imaging agent, it has 2 important disadvantages: (1) soft tissue attenuation and scatter of the low photon energy emission (80 keV); and (2) a relatively long half-life (73 hours). The recent introduction of technetium-99m (Tc-99m)-labeled sesta methoxyisobutyl isonitrile (sestamibi) as a new myocardial imaging agent overcomes these disadvantages, and early comparative studies have shown it to be at least as good as Tl-201 for the detection of myocardial ischemia.¹⁻⁴

Another distinguishing characteristic of Tc-99m sestamibi is that it is fixed in the myocardial cell after uptake with no significant redistribution, unlike Tl-201, which begins to redistribute immediately. In addition to providing high quality planar images of regional myocardial perfusion, the higher photon yield and myocardial fixation of Tc-99m sestamibi allow electrocardiographic gated images to be obtained, thereby providing simultaneous global ventricular function and regional wall motion data. The acquisition of gated images further allows the examination of static perfusion images at different phases in the cardiac cycle, which can avoid the loss of resolution imposed by cardiac motion.

We present some new planar imaging data and review the available data on the accuracy of planar myocardial perfusion imaging and ventricular function assessment with Tc-99m sestamibi.

METHODS

Patients: Seventy patients (61 men, 9 women) and 12 control subjects (10 men, 2 women) form the basis of this study. All patients had either typical angina or atypical symptoms in the presence of significant risk factors for CAD. Coronary angiography was performed within 4 weeks of the radionuclide perfusion studies. Sixty patients had documented coronary artery stenosis (>50% luminal diameter narrowing). One-vessel disease was present in 14 of these patients, 2-vessel disease in 27 and multivessel disease in 19. Ten patients had normal coronary arteriograms. The 12 control subjects were all asymptomatic, had normal resting and exercise electrocardiograms (ECGs) and thus a low probability of CAD.

Exercise testing: Exercise tests were carried out after a 3- to 4-hour fast using a bicycle ergometer. Treatment with β blockers was stopped 48 hours before exercise, unless clinically contraindicated. Testing was maximal

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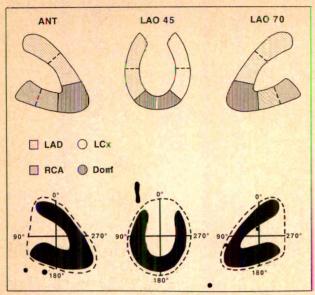


FIGURE 1. Myocardial segmental analysis. Top: left ventricular segments in anterior (ANT), left anterior oblique (LAO) 45° and LAO 70° views. Bottom: division of left ventricle for construction of uptake profiles. Dom = dominant; LAD = left anterior descending; LCx = left circumflex; RCA = right coronary artery. (Reproduced with permission from Int J Cardiol. 12)

(symptom-limited) and graded, starting at a level of 25 watts (150 kpm) and increased by 25 watts every 2 minutes. Throughout the test, continuous 3-channel electrocardiographic monitoring was performed using leads II, V₁ and V₅. A 12-lead ECG was recorded at rest, after every 2 minutes of exercise, at the onset of angina, at peak exercise and every minute for the first 5 minutes of recovery. End points for the exercise tests were angina of increasing severity, horizontal or down-sloping ST-segment depression of >3 mm, a decrease in systolic blood pressure of >20 mm Hg or a significant exercise-induced arrhythmia. For paired studies, the second exercise test was performed to the same level as assessed by peak heart rate and blood pressure response.

Thallium-201 imaging: At peak exercise, 74 MBq (2 mCi) of Tl-201 was injected intravenously and the patient was exercised for a further 1 to 2 minutes at a lower workload. Imaging commenced 5 to 10 minutes after injection. Using a general all-purpose collimator, we obtained three 10-minute views (anterior, left anterior oblique [LAO] 45° and LAO 70°). Delayed imaging was performed at 4 hours using the same protocol.

Technetium-99m sestamibi imaging: A dose of 400 to 600 MBq (10 to 16 mCi) of Tc-99m sestamibi was injected intravenously at peak exercise and the patient exercised for a further 1 to 2 minutes at a lower workload. The patient was given a meal, and we began imaging 1 hour after injection using the same parameters as for Tl-201 imaging. Rest images were usually obtained 48 hours later using a second, similar (<5% difference) dose of Tc-99m sestamibi. When cardiac gating was used, 18 frames/cardiac cycle in a 64 × 64 matrix were acquired.

Image display and analysis: The images were displayed on the video monitor in color and black and white monochrome with the myocardial image normalized to the highest count rate within the myocardium. Images were evaluated both unprocessed and after interpolated background subtraction.6

Qualitative image analysis was performed by 3 observers without knowledge of the patient's coronary anatomy. Each of the 3 views was divided into 5 segments (Fig. 1, top), and left ventricular (LV) myocardial uptake of each radiotracer was evaluated on a 3-point scale (normal, decreased or absent) for each segment. A similar 3point scale (complete, partial or absent) was used to evaluate defect reversibility using delayed Tl-201 images or resting Tc-99m sestamibi images. Results were reached either by consensus of all 3 observers or by majority

We carried out semi-quantitative image analysis using the myocardial uptake of each 10° radial segment. These images were normalized to the area of maximum intensity and maximal count uptake curves were plotted (Fig. 1, bottom). For the exercise and resting images of Tc-99m sestamibi, any segment with >70% of maximum activity level was considered normal. For Tl-201, a standard "normal distribution" uptake curve was used. For both agents, reversibility was considered significant when improvement in relative segmental uptake was equal to or exceeded a 20% increase between exercise and delayed (or resting) images.

Cardiac and lung uptake ratios: Measurements of lung and right ventricular uptake of both radiotracers were expressed as a ratio to maximal LV uptake (Fig. 2). Regions of interest were selected manually in the upper zone of the left lung and the area of the LV myocardium with maximal counts in the anterior view. These were expressed as a lung uptake ratio ("lung index"). The right ventricular uptake ratio was similarly determined from the myocardial segment, with maximal counts in the right ventricle and the segment in the left ventricle with maximal activity in the LAO 45° view ("right ventricular index").

Upper normal limits for myocardial and lung indexes for Tl-201 and Tc-99m sestamibi were defined as the

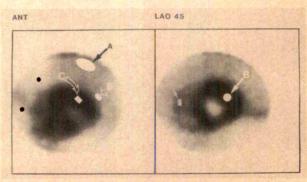


FIGURE 2. Areas of interest for the measurement of lung and right ventricular uptake ratios. Abbreviations as in Figure 1. (Reproduced with permission from Int J Cardiol. 12)

mean +2 standard deviations of the control group. Exercise and resting myocardial uptake ratios for each of the radiotracers were compared using the paired Student *t* test. Comparison of proportions was performed by chisquare or Fisher's exact test.

Gated perfusion images: To evaluate the contribution of gated images to the identification of perfusion defects, the 18 images of each view were displayed (Fig. 3) and the 2 most visually prominent images of end-diastole (ED) were combined to create 1 static end-diastolic image. Similarly, the 2 most prominent end-systolic images were combined to create 1 static end-systolic image. The ungated images were created by combining all 18 frames to produce 1 static ungated image. These 3 images were background subtracted, interpolated and smoothed by a 9-point smooth program and normalized to the pixel with the highest count ratio in the myocardium. The 3 static images (i.e., end-diastolic, end-systolic and ungated) were displayed on a monitor and observed by 3 independent observers. For each view, the 5 segments (total of 15) were graded for perfusion abnormalities on a scale of 0 to 4: grade 0 = definitely normal, grade 1 = probably normal, grade 2 = possibly abnormal, grade 3 = probably abnormal and grade 4 = definitely abnormal.

Ventricular functional assessment: From the gated LAO images of the left ventricle, anterior to posterior wall (AP) and septum to lateral wall (SL) dimensions of the cavity were measured by counting the number of pixels along each axis to the inner edge of the myocardium defined subjectively by the observer at both ED and end-systole (ES) (Fig. 4). "Radionuclide fractional shortening" (RFS) was calculated for each axis: RFS (%) = [(ED - ES)/ED] × 100.

A gobal measure of RFS was derived: Global RFS

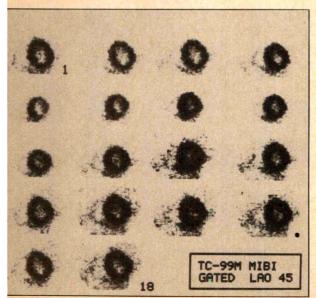


FIGURE 3. Eighteen images of the gated LAO 45° view. LAO-= left anterior oblique; MIBI = methoxyisobutyl isonitrile; Tc-99m = technetium-99m. (Reproduced with permission from Eur Heart J.⁵)

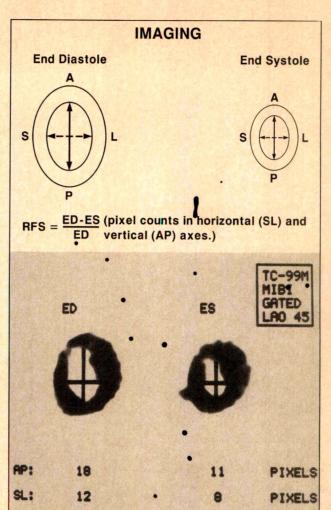


FIGURE 4. Top: left ventricular radionuclide fractional shortening (RFS) measurements from gated end-diastolic (ED) and end-systolic (ES) perfusion images. Bottom: Tc-99m sestamibi scintigrams from a patient with ischemic heart disease.

A = anterior; L = lateral; P = posterior; S = septum; other abbreviations as in Figure 3. (Reproduced with permission from Eur Heart J.5)

(%) = $[(ED_{AP} + ED_{SL}) - (ES_{AP} + ES_{SL})/(ED_{AP} + ED_{SL})] \times 100$.

A second method applied a semi-automatic fitting of an ellipse to the inner wall of the left ventricle. The ellipse was controlled by the observer to provide the "best fit" to the cavity. The area of the ellipse in diastole and systole was then used as in index of LV function (LVI): LVI (%) = [(ED area - ES area)/ED area] × 100.

The 18 gated images were displayed as a continuous cine loop on the video monitor for the qualitative evaluation of global and regional ventricular function.

Gated blood pool equilibrium studies: Eighteeen patients underwent resting Tc-99m radionuclide ventriculography using red blood cells labeled in vivo. LV ejection fraction (EF) from the LAO 45° projection was calculated using a standard semi-automated program. Regional wall motion was assessed visually from the cine display.

	Total		Mean/Pat	ient (± SD)	
	TI-201	Tc-99m Sestamibi	TI-201	Tc-99m Sestamibi	
Qualitative analysis					
Exercise	190	225	4.8 ± 2.1	5.6 ± 2.5	
Delayed/rest	119	82	3.0 ± 2.1	2.1 ± 2.0	
Quantitative analysis					
Exercise	201	226	5.0 ± 2.6	5.7 ± 3.2	
Delayed/rest	148	115	3.7 ± 2.2	2.9 ± 2.3	

Echocardiographic studies: M-mode echocardiography for measurement of LV fractional shortening was performed 45 minutes after Tc-99m sestamibi injection, before gated radionuclide image acquisition. Recordings were taken at a level just below the mitral valve leaflets, and only those containing clear, simultaneous echoes of the septum and posterior wall were used for analysis. Results of the radionuclide measurements were compared with those of echocardiographic fractional shortening using linear regression analysis. Echocardiographic fractional shortening and LVEF measured by the blood pool equilibrium study were also compared with global RFS.

Coronary arteriography: Coronary arteriography was performed using the Sone's technique. The coronary arteries were imaged in multiple views, and the arteriograms were analyzed qualitatively by two experienced observers. LV function was graded on a scale of 0 to 4: grade 0 = normal, grade 1 = hypokinesis limited to one segment, grade 2 = akinesis limited to one segment, grade 3 = hypokinesis or akinesis involving two or more segments, and grade 4 = grade 3 plus one or more areas of frank dyskinesis.

Statistical analysis: Proportional comparisons were by chi-square or Fisher's exact tests as appropriate. Differences between groups were assessed by the Student t test.

RESULTS

Semi-quantitative assessment: Fifty-two subjects were studied (44 men, 8 women). Forty were CAD patients (mean age 55 ± 9 years) and 12 were asymptomatic control subjects (mean age 25 ± 4 years).

The results of both qualitative and quantitative methods as the total and mean number of segments with decreased or absent perfusion at exercise or delayed Tl-201 and rest Tc-99m sestamibi images are listed in Table I. The number of segments with reversible uptake defects was recorded For the qualitative analysis, the exercise images showed decreased tracer uptake in 225 segments for Tc-99m sestamibi and 190 segments for Tl-201, with concordant abnormalities in 169 segments (89%).

The perfusion defects were fully or partially reversible in 143 segments (35 patients) for Tc-99m sestamibi and 71 segments (28 patients) for Tl-201.

Using the semi-quantitative method, the exercise images showed decreased radiotracer uptake in 226 segments for Tc-99m sestamibi and 201 segments for Tl-201, with concordant abnormalities in 183 (91%) segments. The perfusion defects were fully or partially reversible in 111 segments (30 patients) for Tc-99m sestamibi and 53 segments (27 patients) for Tl-201.

Analysis of the regional distribution of myocardial perfusion defects on the exercise scintigrams permitted identification of the diseased vessel in the majority of cases. Ninety-three percent of diseased left anterior descending arteries were correctly identified, compared with 89% of right arteries and 83% of circumflex coronary arteries.

Qualitative and quantitative analyses of exercise and resting images showed homogeneous radiotracer uptake in all patients without significant CAD, except 2 in whom an anterolateral defect occurred during exercise with partial reversibility on resting images. There were no false positives in the asymptomatic control group (normalcy rate of 100%).

Gated perfusion images: Twenty-two patients were evaluated who had gated exercise Tc-99m sestamibi studies done, with a total of 330 segments analyzed. The end-diastolic or gated images showed a greater frequency of segments with visual perfusion defects (129 of 330, 39%) as compared to the ungated images (85 of 330, 26%). Qualitative defects were also identified with a higher level of confidence. This is reflected in the scoring for the gated versus the ungated studies (grade 3: 52 vs 21; grade 4: 33 vs 15). The true-positive rates (defined by angiographic narrowing of >50%) for grade 4: 30 gated vs 16 ungated; grades 3 + 4: 68 vs 39; and grades 2 + 3 + 4: 113 vs 79.

Plotting the results as a receiver operating characteristic (ROC) curve (Fig. 5) confirmed that gated exercise end-diastolic images revealed an improved performance for the detection of CAD compared to ungated images. The area under the ROC curve for end-diastolic images equals 0.81; that for ungated images, 0.73.

Lung uptake: Fifty-two patients were studied. Forty (34 men, 6 women, mean age 55 ± 9 years) had typical

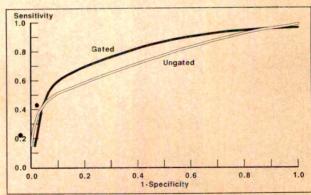


FIGURE 5. Receiver operating characteristic (ROC) curve analysis for the detection of ischemic segments as shown by angiographic lesion >50%. Comparison of gated and ungated images.

angina and angiographically proven CAD. The remaining 12 patients comprised the asymptomatic control group.

In the control group, resting lung index was $36 \pm 9\%$ for Tc-99m sestamibi. Exercise caused a small but insignificant reduction in this value ($32 \pm 5\%$).

Table II lists the results for the CAD patients. The mean value for resting Tc-99m sestamibi lung index in the CAD patients (35 \pm 6%) was similar to that obtained in the control group. However, unlike the control group, lung uptake increased with exercise in nearly 50% (19 of 40) of the CAD patients. The mean exercise lung index for CAD patients (36 \pm 8%) was significantly higher than in patients with normal coronary arteries (32 \pm 5%, p <0.01).

If the upper limit of normal for exercise Tc-99m sestamibi lung index is defined as 42% (mean \pm 2 standard deviations), 8 CAD patients had an abnormally elevated Tc-99m sestamibi exercise lung index. Those patients with an abnormal lung index had more-extensive CAD than the remainder of the group (2.5 \pm 0.3 diseased vessels/patient vs 1.75 \pm 0.4).

Tl-201 lung index was significantly lower on exercise than on delayed images in the CAD group. There was no significant difference between the exercise and delayed Tl-201 lung indices in the control group ($39 \pm 7 \text{ vs } 42 \pm 7\%$). In both the CAD and control groups, exercise Tl-201 lung indices were significantly higher than the corresponding indices for Tc-99m sestamibi.

Abnormal exercise Tl-201 lung index was defined as being >53%. This is similar to the definition of abnormality adopted by Brown et al. Exercise Tl-201 lung index was abnormal in 6 CAD patients. Five of these 6 patients also had an abnormal exercise Tc-99m sestamibi lung index (concordance of 83%).

Right ventricular uptake: In the control group, the resting right ventricular index was $42 \pm 7\%$ for Tc-99m sestamibi. Exercise did not significantly affect this value $(44 \pm 6\%)$.

Right ventricular uptake of Tc-99m sestamibi in the CAD patients was similar to that for the control subjects at rest $(43 \pm 7\%)$, but increased significantly with exercise $(48 \pm 9\%, p < 0.01)$. If the upper limit of normal for Tc-99m sestamibi exercise right ventricular index is defined as 56%, right ventricular index was abnormally

TABLE II Exercise and Delayed/Rest Lung and Right Ventricular Indices (Mean ± SD) for TI-201 and Tc-99m Sestamibi Images in Patients with Coronary Artery Disease

	Lung Index		Right Ventricul	ar Index
	TI-201	Tc-99m Sestamibi	TI-201	Tc-99m Sestamibi
Exercise (%)	40 ± 10	36 ± 8	56 ± 9	48 ± 9
Delayed/rest (%)	47 ± 9	35 ± 6	57 ± 8	43 ± 7
p value	< 0.01	NS	NS	< 0.001

increased in 6 patients. Those patients with abnormal elevation of the Tc-99m sestamibi right ventricular index had more extensive CAD than the remainder of the group $(2.83 \pm 0.2 \text{ diseased vessels/patient vs } 1.73 \pm 0.5, \text{ p} < 0.05)$. The abnormal elevation in right ventricular index in these patients occurred despite significant right coronary stenoses in all 6 cases.

Mean right ventricular index for Tl-201 was similar for exercise and delayed images, both in the control group $(53 \pm 6 \text{ and } 55 \pm 7\%, \text{ respectively})$ and in the CAD group $(56 \pm 9 \text{ and } 57 \pm 8\%, \text{ respectively})$. Exercise Tl-201 right ventricular index was abnormal (>65%) in 5 of the 6 patients with an abnormal Tc-9m sestamibi right ventricular index.

Gated functional studies: A total of 106 Tc-99m sestamibi studies (46 after exercise, 60 resting) were performed in 68 patients. Eight studies in 6 patients could not be analyzed because of technical limitations inherent in the method: in 3 patients, full thickness infarction and complete absence of regional tracer uptake made it impossible to define the LV cavity dimensions in 1 or both axes; 2 patients with systolic cavity obliteration prevented measurement of the end-systolic dimension; and in 1 ectomorphic patient, the vertical position of the heart distorted the radionuclide image of the left ventricle and made measurement of the vertical axis impossible. Thus, 96 studies in 62 patients are the subject of this report.

RFS was $36 \pm 11\%$ (mean \pm standard deviation) (range 13 to 55%) in the vertical axis and $33 \pm 10\%$ (range 7 to 64%) in the horizontal axis. Echocardiographic fractional shortening in the same patients was $37 \pm 9\%$ (range 15 to 55%). Regression analysis showed a good correlation between the 2 methods, with the AP axis measurements showing the best correlation (r = 0.89, p <0.001).

The global RFS (derived from both the vertical and horizontal axis measurements) was $35 \pm 10\%$ (range 14 to 59%), and this correlated well with echocardiographic fractional shortening (r = 0.85, p <0.001) as defined by the regression equation: RFS = $2.2 + 0.90 \times$ echocardiographic fractional shortening (Fig. 6).

Radionuclide ventriculography (RNV) in 18 patients showed a mean LVEF of 48% (range 18 to 72%). The global RFS in the same 18 patients was 34% (range 15 to 54%), and regression analysis confirmed a close linear correlation between the 2 variables (r = 0.83, p < 0.001) defined by the equation: RFS = $1.9 + 0.68 \times EF$ (Fig. 7).

Reproducibility measurements were carried out on 30 studies by 2 observers. Interobserver variability was <8% and intraobserver variability <5% for the RFS measurements in the 2 axes.

The study was repeated in 70 patients using the semiautomatic ellipse method and correlated with the angiographic EF (correlation coefficient = 0.91) and with gated blood pool radionuclide EF (correlation coefficient = 0.86).

The qualitative cine display of the gated Tc-99m sestamibi studies was compared with the gated blood pool studies and with angiography for the assessment of regional wall motion abnormalities in 31 patients with pre-

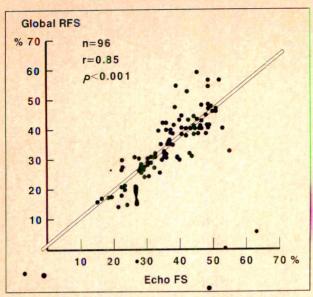


FIGURE 6. Global radionuclide fractional shortening (RFS) compared to echo fractional shortening (FS) in 96 studies. (Reproduced with permission from Eur Heart J.5)

vious myocardial infarction. Tc-99m sestamibi perfusion imaging identified 29 of 31 patients with myocardial infarction (Table III) and was correctly localized to the angiographically akinetic or hypokinetic segments. Eighty-four percent of these patients had both perfusion defects and regional wall motion abnormalities on gated Tc-99m sestamibi studies. When segmental analysis was applied, the gated Tc-99m sestamibi study underestimated the number of abnormal segments as compared with RNV (172 vs 186). For each category (normal, hypokinetic and akinetic) there was concordance between abnormal RNV segments and Tc-99m sestamibi segments in 87% of the segments and a discordance in 13% of the segments. Discordance was due to both overestimation and underestimation of wall motion abnormalities.

DISCUSSION

The clinical application of Tc-99m sestamibi to the diagnosis of ischemic heart disease will depend partly on its diagnostic sensitivity for CAD relative to Tl-201, the established perfusion imaging agent, and also on the benefits related to its advantageous physical and biological properties. We have compared Tc-99m sestamibi and TI-201 in patients with angiographically proven CAD. Qualitative and quantitative image analysis showed concordance in excess of 88% for the identification of ischemic segments. These data, together with studies from other centers, 1,3,4 show that both perfusion imaging agents have a similar sensitivity for the detection of myocardial ischemia.

Studies comparing the accuracy of Tl-201 and Tc-99m sestamibi for the detection of myocardial ischemia using planar imaging have been undertaken in Europe and North America. Three substantial published series are available, 1,3,4 evaluating a total of 174 patients. A further 56 patients from an unpublished European multi-

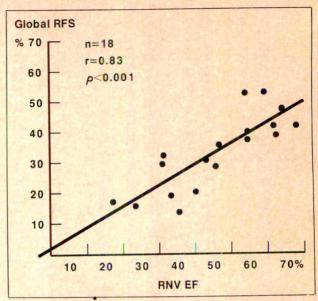


FIGURE 7. Correlation of global radionuclide fractional shortening (RFS) with equilibrium radionuclide ventriculography (RNV) gated ejection fraction (EF) measurements. (Reproduced with permission from Eur Heart J.5)

	Segments			
	Akinetic	Hypokinetic	Normal	
RNV	73	113	189	
Gated Tc-99m sestamibi	69	103	203	

center study are included in this report together with preliminary results from the European and North American Phase III Multicenter trial, adding a further 361 patients. These results are compared in Table IV. The average sensitivity for the diagnosis of CAD using Tc-99m sestamibi is 85% (range 73 to 96%). When individual vessels are considered, this average sensitivity value is reduced to 65% (range 60 to 70%). No significant differences between Tl-201 and Tc-99m sestamibi are shown. Patient and segmental concordances between the 2 agents are high but decline slightly when ischemic or scar patterns are evaluated. However, there is no consistent bias in the studies toward an increased frequency of reporting a scar or a viable segment for either radiopharmaceutical. These results support the initial impression that using planar imaging Tc-99m sestamibi is at least as good as Tl-201 for the diagnosis of ischemic heart disease using similar imaging protocols.

We have used conventional methodology for comparing the sensitivities of Tl-201 and Tc-99m sestamibi in the diagnosis of CAD. For Tl-201, redistribution images were used for the assessment of defect reversibility, while resting images were obtained 24 to 48 hours after the exercise study for Tc-99m sestamibi because this agent shows no significant redistribution. Tc-99m sestamibi provides a true resting (as opposed to redistribution) image of superior quality, and the finding that it identified

TABLE IV Comparison of Results of Multicenter Trials Sensitivity % (No.) Specificity % (No.) Pts Vessels Pts Concordance % Vessels Investigators TI-201 MIBI TI-201 MIBI TI-201 MIRI TI-201 Pts Segments Pattern Wackers et al 97 38 89 Too few 78 76 1989 (35/36)(32/36)(45/65)(39/65)(40/49)(38/49)Kiat et al 1989 36 73 54 50 75 73 60 73 86 91 (19 Angio) (11/15)(11/15)(19/35)(21/35)(2/4) (3/4)(16/22)(19/22)Taillefer et al 1989 100 Not given 70 Not given 89 92 Not given 88 (65 Angio) (72/97)(68/97) Phase II Europe 68 56 98 96 68 Too few 56 58 81

(74/109)

100

93

Normalcy rate (pts): MIBI = 94% (n = 16/17); TI-201 = 88% (n = 15/17).

86

Phase III[†] Europe

Phase III[†] US and

Canada

MIBI = technetium-99m sestamibi; TI-201 = thallium-201; Pts = patients; US = United States

(53/54)

86

80

(52/54)

86

81

(74/109)

significantly more reversible perfusion defects than Tl-201 in part may reflect the greater sensitivity of rest injection images for the detection of reversible myocardial ischemia. Quantitative analysis is likely to further improve the accuracy of planar imaging, and current results together with other published data support this conclusion. However, as has been pointed out by others, 3.8 it will be important to establish background subtraction programs and normal databases specific for Tc-99m sestamibi and not simply rely on data acquired from Tl-201 studies.

Image quality is superior with Tc-99m sestamibi for both the exercise and resting studies because of the better imaging characteristics of the Tc-99m label and the larger doses that can be administered for similar patient radiation doses. This in itself results in a higher diagnostic confidence and probably a quicker learning curve.

Routine gating of the myocardial images permits a more comprehensive evaluation of myocardial perfusion and function without significantly altering the acquisition times. Thus, increased sensitivity can be expected by viewing and measuring the distribution of myocardial perfusion in systole and diastole in addition to the time-integrated image, thus permitting evaluation of defects without the loss of resolution inevitable from the integrated image. Information about wall thickening may also be gained, although this was not evaluated in our study.

In addition to enhancing the perfusion images, routine gating permits the simultaneous assessment of ventricular function because imaging with Tc-99m sestamibi provides adequate edge definition for quantitative evaluation of LV contractile function in the majority of patients. Measurement of RFS using both methods has shown a close correlation with other noninvasive indices of LV function that are accepted methods for the evaluation of myocardial performance.

The relatively low energy of Tl-201 and the low count density of Tl-201 images mitigate against clear edge definition, which is necessary to accurately measure the changes in LV cavity dimensions in diastole and systole

and to produce reliable functional assessment. The higher energy, increased counting statistics and very slow washout from the myocardium of Tc-99m sestamibi overcome these inherent disadvantages of Tl-201.

(34/59)

(33/59)

An important limitation of echocardiographic fractional shortening measurements is that ventricular function is evaluated only in 1 dimension. To diminish this limitation, we measured the RFS in 2 dimensions and derived the global fractional shortening by averaging the 2 measurements. The global fractional shortening, like the 2 variables from which it was derived, showed a close correlation with the echocardiographic fractional shortening. More importantly, the global RFS showed a close correlation with the LVEF in those patients who underwent RNV. Radionuclide EF is a well-established measure of LV contractile function. It is a volume-related parameter because it is count-based, and exact correlation with the linear-based global fractional shortening method would not be expected. However, the close correlation of EF with global fractional shortening suggests a potentially useful clinical role for this new ejection phase variable as an adjunct to perfusion measurements.

Interobserver variability for the RFS determinations was low, enhancing the clinical validity of this new measurement. Nevertheless, this method has technical limitations that occasionally prevented complete quantitative assessment. In certain patients, LV delineation was impossible due to either systolic cavity obliteration or the absence of regional uptake in areas of extensive full thickness infarction. However, these technical limitations do not detract significantly from the clinical application of the method since we found them to be relatively uncommon in practice. The main drawback is that there is not a true inner circumference using planar imaging; single photon emission computed tomographic imaging, which uses a true slice and therefore an inner circumference, may further improve the usefulness of cardiac gating.

Tl-201 exercise lung index is a useful diagnostic indicator, abnormal elevation being associated with extensive CAD. 10 Exercise may cause exertional LV dysfunction

and prolong pulmonary transit time, thereby enhancing pulmonary extraction of the isotope. Our results suggest that Tc-99m sestamibi lung index may be influenced by the same factors. Thus, Tc-99m sestamibi lung index tended to increase with exercise in many CAD patients (reflecting exertional LV dysfunction), but showed a decrease in the control group. Patients with abnormal elevation of the Tl-201 exercise lung index also had abnormal elevation of the Tc-99m sestamibi lung index, and all these patients had extensive CAD. Two of the remaining 34 patients with normal exercise Tl-201 lung index had an abnormal Tc-99m sestamibi lung index. In both cases, this was associated with 3-vessel CAD. Although the number of patients with abnormal elevation of the Te-99m sestamibi exercise lung index was small, our data do suggest that routine measurement of this variable might improve the specificity of perfusion imaging for the diagnosis of CAD. Further assessment of the degree of increased lung uptake of Tc-99m sestamibi immediately after exercise (as opposed to 1 hour later) would be of

The lung and right ventricular uptakes of both Tl-201 and Tc-99m sestamibi appeared to be governed by similar factors in the CAD patients, with higher values associated with exercise compared with at rest. However, in the control group, there was no significant difference between the exercise and resting values. Again, it was the patients with extensive CAD who tended to have higher values for the exercise right ventricular index. Pulmonary hypertension and right ventricular hypertrophy are associated with increased resting right ventricular uptake of Tl-201,9 and right ventricular uptake defects with exercise are thought to predict proximal right coronary disease.11 Nevertheless, the mechanism and diagnostic significance of exertional changes in right ventricular Tc-99m sestamibi uptake observed in our patients are undetermined. Similar to lung uptake, the data may provide an indication of the severity of CAD.

Planar myocardial imaging may eventually be superceded by single photon emission computed tomography imaging. However, currently, the vast majority of clinical studies are performed using a planar camera. Moreover, planar camera studies are easier to perform, require less quality control and give rise to fewer artifacts. The data presented in this study and those from other planar imaging studies suggest that planar imaging with Tc-99m sestamibi is at least as accurate as Tl-201 for the detection of CAD in patients and in individual vessels. Furthermore, the improved image quality of the Tc-99m sestamibi studies appears to improve observer confidence in the interpretation of the myocardial perfusion scintigrams. Thus, Tc-99m sestamibi seems likely to replace Tl-201 for many purposes in the investigation of CAD. Performing a comprehensive evaluation of perfusion, including gated diastolic and systolic images, wall motion studies and uptake ratios of the lungs and right ventricle, will maximize the data derived from studies using this important new agent.

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Myocardial Perfusion Imaging with Technetium-99m Sestamibi SPECT in the Evaluation of Coronary Artery Disease

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Technetium-99m (Tc-99m) sestamibi is a new myocardial perfusion imaging agent that offers significant advantages over thallium-201 (TI-201) for myocardial perfusion imaging. The results of the current clinical trials using acquisition and processing parameters similar to those for TI-201 and a separate (2-day) injection protocol suggest that Tc-99m sestamibi and TI-201 single photon emission computed tomography (SPECT) provide similar information with respect to detection of myocardial perfusion defects, assessment of the pattern of defect reversibility, overall detection of coronary artery disease (CAD) and detection of disease in individual coronary arteries. Tc-99m sestamibi SPECT appears to be superior to Tc-99m sestamibi planar imaging because the former provides a higher defect contrast and is more accurate for detection of disease in individual coronary arteries. Research is currently under way addressing optimization of acquisition and processing of Tc-99m sestamibi studies and development of quantitative algorithms for detection and localization of CAD and sizing of transmural and nontransmural myocardial perfusion defects. It is expected that with the implementation of the final results of these new developments, further significant improvement in image quality will be attained, which in turn will further increase the confidence in image interpretation. Development of algorithms for analysis of end-diastolic myocardial images may allow better evaluation of small and nontransmural myocardial defects. Furthermore, gated studies may provide valuable information with respect to regional myocardial wall motion and wall thickening. With the implementation of algorithms for attenuation and scatter correction, the overall specificity of Tc-99m sestamibi SPECT should improve significantly because of a substantial decrease in the occurrence of attenuation-related image artifacts. Simultaneous assessment of ventricular function by performing first-pass studies may provide important additional information to that obtained from analysis of procardial perfusion.

(Am J Cardiol 1990;66:55E-62E)

Technetium-99m (Tc-99m) sestamibi¹ is a new myocardial perfusion imaging agent with physical characteristics superior to those of thallium-201 (Tl-201). Compared to Tl-201, the shorter half-life (6 hours) of Tc-99m sestamibi, coupled with its prompt hepatobiliary and renabexcretion, results in more favorable radiation dosimetry. Approximately 10 times the dose of Tl-201 can be administered for similar radiation exposure. The higher injectable dose also allows first-pass² studies and cardiac gating³ for the assessment of ventricular function and wall motion. In addition, due to its photon energy of 140 keV, which is optimal for standard gamma camera imaging, better overall image quality has been demonstrated compared with Tl-201.⁴

Recently, single photon emission computed tomography (SPECT) has been widely used as an imaging modality because it provides a higher defect contrast and better resolves overlapping myocardial regions than conventional planar imaging. Both characteristics improve the detection and localization of coronary artery disease (CAD). 5-7 We review several aspects of myocardial perfusion imaging using Tc-99m sestamibi and SPECT.

TECHNETIUM-99m SESTAMIBI TOMOGRAPHY VERSUS THALLIUM-201 TOMOGRAPHY FOR MYOCARDIAL PERFUSION IMAGING

After initial clinical trials that established the safety of Tc-99m sestamibi in humans, 8 extensive clinical information has been generated on the clinical utility of Tc-99m sestamibi myocardial perfusion SPECT imaging through the North American Multicenter Clinical Trial and studies by several investigators. 4,10,11 In the Phase III Multicenter North American Clinical Trial, 22 centers in the United States and 2 centers in Canada participated in an open-label study designed to compare Tc-99m sestamibi with Tl-201 imaging and coronary angiography. All patients underwent maximal exercise Tl-201 and Tc-99m sestamibi SPECT studies separated by an average of 4

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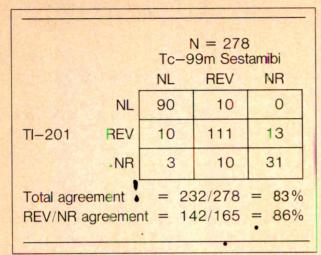


FIGURE 1. Agreement between technetium-99m (Tc-99m) sestamibi and thallium-201 (TI-201) for classification of normal images (NL), and images with reversible (REV) and those with nonreversible (NR) defects, in 278 patients. REV/NR = the agreement for pattern of reversibility (reversible or nonreversible). The numerator is the number of patients with stress defects present in both Tc-99m sestamibi and TI-201 images.

days. Separate rest and exercise Tc-99m sestamibi SPECT studies were performed on 2 days using an average of 20 mCi for each injection. Coronary angiography was performed within an average of 16 days of the Tc-99m sestamibi study. Of the 278 patients in the study population, 39 had normal coronary arteriograms, 153 had angiographically documented CAD and 86 had <5% likelihood of coronary disease based on Bayesian analysis of their age, sex, clinical symptoms and the results of exercise electrocardiography. 12-14 For the evaluation of agreement between Tc-99m sestamibi and Tl-201 SPECT studies, and for the correlation with the results of coronary arteriogram, all perfusion images were visually analyzed by blinded interpretation of investigators in each participating institution for the presence of myocardial perfusion defects and the pattern of defect reversibility. Some of the results from the Multicenter Trial are summarized in the present report.

Agreement for presence of stress defect: Of the 278 patients, 255 (92%) were concordant with respect to the presence or absence of stress perfusion defects. The agreement between the 2 agents was further assessed on a segment-by-segment basis. Of all the SPECT myocardial segments evaluated (6,677 segments), 4,943 were concordantly interpreted as normal and 1,191 were concordantly interpreted as abnormal with perfusion defects, resulting in a segmental agreement of 92%.

Assessment of stress defect reversibility: To assess the efficacy of Tc-99m sestamibi in the evaluation of myocardial viability, the patterns of stress defect "reversibility" from perfusion images of the 2 tracers were compared. Of note, the mechanism for stress defect reversibility of Tc-99m sestamibi is different from that of Tl-201. Reversibility of Tl-201 defect is the result of the differential washout rate of Tl-201 from the normal and viable but hypoperfused myocardial regions. Unlike Tl-201,

however, Tc-99m sestamibi does not appear to have significant myocardial redistribution. ^{15,16} Therefore, for the assessment of defect reversibility by Tc-99m sestamibi 2 separate injections are required, 1 at peak exercise and the other at rest. While images acquired after injection of Tc-99m sestamibi at peak stress demonstrate exercise-induced disparity of regional myocardial blood flow, images obtained after injection at rest show the pattern of myocardial perfusion in the resting state.

Improvement or normalization of an exercise defect on the resting image indicates defect reversibility and implies the presence of viable but hypoperfused myocardium. Figure 1 summarizes the agreement between Tl-201 and Tc-99m sestamibi in 278 patients with respect to differentiation of normal, reversible and nonreversible patterns.8 To categorize images according to the stress defect reversibility pattern, patients who had images with stress defects without evidence of reversibility were categorized into the nonreversible subgroup, while patients who had images demonstrating reversible defects (with or without nonreversible defects) were categorized into the reversible subgroup. Images with no stress defects were classified as normal. The exact agreement was 83% (232 of 278). In addition, of the 165 patients with perfusion images demonstrating stress defects by both agents, 142 (86%) were concordant with respect to differentiating reversible from nonreversible patterns. When analysis was performed on a segment-by-segment basis, there was 89% exact agreement between Tc-99m sestamibi and Tl-201 for normal, reversible and nonreversible defects. Finally, of 1,191 segments that showed stress defects by both agents, 84% were concordant for differentiation of reversible from nonreversible patterns. In the discordant segments, defects that were reversible by Tc-99m sestamibi but nonreversible by Tl-201 predominated.

Detection of angiographic coronary artery disease: The diagnostic accuracy of Tc-99m sestamibi and Tl-201 SPECT images for the identification of patients with CAD was evaluated in 192 patients who had coronary angiography. Among the 153 patients with CAD (>50% luminal stenosis), the overall sensitivities of Tc-99m sestamibi and Tl-201 were 89 and 90%, respectively. The overall specificities, determined in the 39 patients who had normal coronary arteriograms, were 49% for Tc-99m sestamibi and 41% for Tl-201. The observed low specificity by both agents is consistent with previously reported specificities for Tl-20117-19 and is most likely due to patient referral bias such that patients with an abnormal perfusion study were preferentially referred to coronary angiography. 14,20,21 Importantly, for both agents, the normalcy rates (defined as the number of patients from the low likelihood group with normal scintigraphic patterns divided by the total number of patients in the low likelihood group) in 86 patients with <5% likelihood of CAD were significantly higher than their respective specificities. For Tc-99m sestamibi, the normalcy rate was 81% and for Tl-201 it was 82%. Thus, from this multicenter study, the results with Tc-99m sestamibi SPECT were similar to those with Tl-201. Of note, however, this trial used acquisition parameters that had been optimized for Tl-201 over several years. As will be discussed, optimiza-

100% 100% 94% SPECT - Planar 90 80 75% 75% 73% 70 60 50 40 30 20 10 n= 0 Sensitivity **Normalcy Rate** Specificity

FIGURE 2. Overall sensitivity, specificity for identification of patients with coronary artery disease (CAD) and normalcy rate in patients with <5% likelihood of CAD.¹⁰

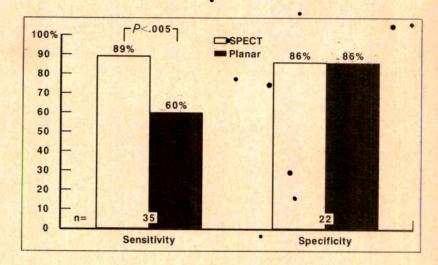


FIGURE 3. Sensitivity and specificity for identification of diseased coronary arteries.¹⁰

tion of Tc-99m sestamibi acquisition may further improve the performance of this new agent.

TECHNETIUM-99m SESTAMIBI TOMOGRAPHY VERSUS PLANAR IMAGING

SPECT is expected to be superior to planar imaging for evaluation of CAD because it provides a higher defect contrast and minimizes regional myocardial overlap. To evaluate the potential superiority of Tc-99m sestamibi SPECT over planar imaging, several comparative studies have been conducted with respect to perfusion defect intensity, detection and localization of CAD. The data are summarized here.

Perfusion defect intensity: Previously it has been observed that on planar images, Tc-99m sestamibi defects may appear less pronounced than Tl-201 defects. To determine the imaging method best suited for Tc-99m sestamibi, differences in perfusion defect intensities between SPECT and planar methods with both radioisotopes were evaluated on a preliminary basis in a group of 9 patients. Defect intensity was defined as the activity in the defect zone divided by the activity in the normal zone. With this definition, the more intense (pronounced) the defect, the lower the value of defect intensity. This preliminary study demonstrated that defects were more pronounced on planar Tl-201 images than the corresponding

planar Tc-99m sestamibi images (75 \pm 7 vs 81 \pm 9, p <0.01). In contrast to planar imaging, comparison of Tc-99m sestamibi and Tl-201 SPECT images in the same group of patients showed that perfusion defect intensities were similar between the 2 agents (60 \pm 21 vs 63 \pm 23, respectively, difference not significant). Overall, the SPECT technique appeared to significantly improve Tc-99m sestamibi defect contrast (or reduce perfusion defect intensity) when compared to planar images (81 \pm 9 vs 63 \pm 23, p <0.05). These findings are being evaluated in a larger group of patients.

Detection and localization of coronary artery disease: In a recent study, ¹⁰ a group of 36 patients underwent Tc-99m sestamibi studies using both SPECT and planar methods. For identification of patients with CAD, the overall sensitivities appeared to be higher by SPECT (93%) compared to planar imaging (73%), but the difference did not reach statistical significance in the small population studied. The overall specificities in patients with normal coronary arteriograms were 75% by both imaging methods. In addition, the study showed that normalcy rates in patients with a low likelihood of CAD were 100% by SPECT and 94% by planar imaging (difference not significant) (Fig. 2). With respect to localization of CAD, the sensitivity of Tc-99m sestamibi SPECT for the detection of disease in individual coronary arteries

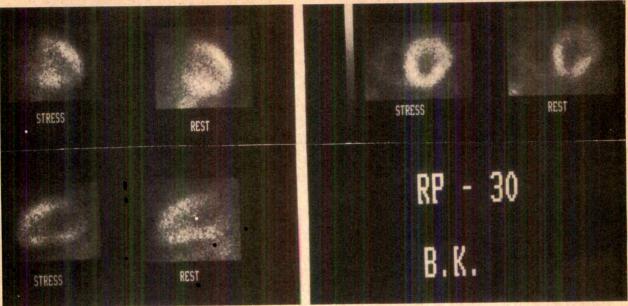


FIGURE 4. Planar images demonstrating reversible inferior wall defects in a patient with 3-vessel disease. (Adapted with permission from Am Heart J.10)

was 89%, which was significantly higher than the 60% obtained by Tc-99m sestamibi planar studies (Fig. 3). The specificity of SPECT and planar Tc-99m sestamibi studies for the detection of disease in individual coronary arteries was 86% for both imaging methods. Similar results with respect to the high diagnostic accuracy of Tc-99m sestamibi SPECT have subsequently been reported by other investigators. 9,11 Figures 4 and 5 show examples of images from a patient with angiographically documented 3-vessel disease who underwent both planar and tomographic Tc-99m sestamibi studies. On the planar images (Fig. 4), a small reversible inferior wall defect is noted, suggesting the presence of single-vessel right coronary artery disease. On the SPECT images (Fig. 5), however, in addition to the reversible inferior wall defect, reversible defects are also noted in the lateral wall and distal anteroseptal regions, correctly suggesting the presence of additional disease in the left circumflex (LCX) and in the left anterior descending (LAD) coronary arteries, respectively.

MIBI

FIGURE 5. Single photon emission computed tomography (SPECT) images of the patient shown in Figure 4. Partial reversible defects are seen in the inferior wall (right coronary artery territory), and lateral wall (left circumflex coronary territory). In addition, a distal reversible defect is seen corresponding to a midleft anterior descending coronary artery disease. (Adapted with permission from Am Heart J.10)

QUANTITATIVE ANALYSIS

As with Tl-201, quantitative analysis is an important adjunct to the interpretation of Tc-99m sestamibi myocardial perfusion images, for the purpose of detecting and localizing CAD, and for the assessment of perfusion defect extent and the evaluation of prognosis.

Detection and localization of coronary artery disease: Kahn et al4 have described a computerized method for quantitative analysis of Tc-99m sestamibi studies using a gender-specific normal database that was established using data obtained from 12 normal volunteers without evidence of organic cardiac disease. The diagnostic accuray of the quantitative technique was evaluated in 36 patients with angiographically documented CAD. The overall sensitivity for detection of CAD was 95%. The sensitivities for detection of disease in LAD, LCX, and right coronary arteries were 74, 91 and 74%, respectively. The respective specificities were 83, 76 and 69%. Using an approach similar to that used for quantitation of Tl-201 SPECT studies, 18,19 a quantitative method has recently been developed by Van Train and associates (unpublished data) at Cedars-Sinai Medical Center for the interpretation of exercise-rest (2-day protocol) Tc-99m sestamibi images. A gender-specific normal database was established using data from patients with <5% likelihood

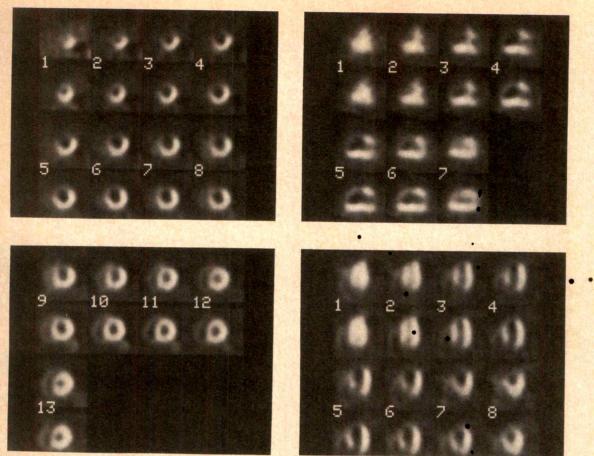
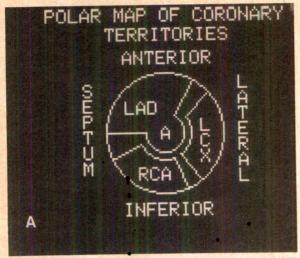


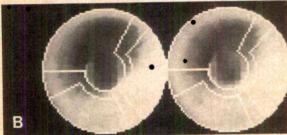
FIGURE 6. Technetium-99m (Tc-99m) sestamibi stress-rest single photon emission computed tomography (SPECT) images from a patient with prior myocardial infarction. Left top and bottom quadrants are the short-axis views, the right top quadrant shows the vertical long-axis views and the right bottom quadrant shows the horizontal long-axis views. First and third rows of each quadrant are the stress tomograms; the second and fourth rows are the corresponding rest tomograms. This study demonstrates anteroseptal and apical stress defects with partial reversibility in the high lateral and proximal anteroseptal walls suggesting periinfarction ischemia. The patient had 1-vessel proximal left anterior descending disease on coronary angiography.

of CAD. Using the same criteria for detection and localization of myocardial perfusion defects on polar map displays as previously described for Tl-201,18 similar sensitivities and specificities were noted for overall detection of disease and detection of disease in coronary arteries to that reported by Kahn et al.4 In a collaborative study between the 2 groups, Kiat et al (unpublished data, 1990) reported application of the Cedars-Sinai Medical Center method to the population from the University of Texas Southwest Medical Center. They showed similar interinstitutional results even though different camera and computer systems were used in the 2 institutions and Cedars-Sinai normal limits were applied. Figures 6 and 7 show images and the results of quantification in a patient with a prior anterior myocardial infarction and significant LAD coronary artery stenosis. Both visually and quantitatively, there are apical and large anteroseptal defects with some reversibility in the high lateral and proximal anteroseptal walls.

Quantification of perfusion defect extent: Another important aspect of quantitative analysis relates to sizing of perfusion defects for the accurate assessment of defect

extent as well as prognosis. It has long been known that prognosis in patients with CAD relates to the extent of ischemic and infarcted myocardium. Several investigators have reported the accuracy of Tc-99m sestamibi myocardial SPECT images for quantification of myocardial perfusion defect size. Verani et al23 studied 13 dogs with permanent coronary occlusion that were imaged with Tc-99m sestamibi SPECT using a 64 × 64 matrix. The percent total left ventricular defect size was defined as the percent of all circumferential count profile points below a 50% threshold. Defect size by Tc-99m sestamibi SPECT correlated highly (r = 0.95) with postmortem pathologic defect size as determined by triphenyltetrazolium chloride (TTC) staining. Gibbons et al24 developed and validated a quantitative technique in a heart phantom in which the SPECT defect size was defined as the area enclosed between the count profiles and a 60% threshold. There was virtually a 1-to-1 relation between the SPECT and true defect size (r = 0.99, y = 1.00x -1.07). This method was then successfully applied to patients with evolving myocardial infarction to assess the effect of thrombolytic therapy in reducing the size of





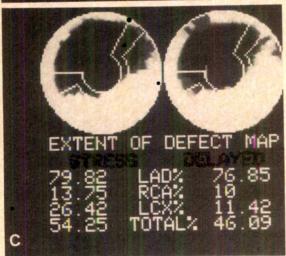


FIGURE 7. Corresponding quantitative technetium-99m (Tc-99m) sestamibi results of the patient in Figure 6. A, Boundaries defining the coronary artery perfusion on the polar map. B, Relative count polar maps for stress (left) and rest (right) tomograms. C, Quantitative results after comparison of the patient's study to the normal limits. The anteroseptal and apical stress defects (left) are confirmed quantitatively with slight improvement on the rest polar map (right) indicating the presence of ischemia.

myocardium at risk.²⁴ Bergin et al²⁵ measured Tc-99m sestamibi myocardial defect size as the percent of profile points below 60% of the peak activity, on the images of excised hearts in experimental animals. Using this technique, they showed a high correlation (r = 0.79) with the area at risk defined anatomically by monastral blue. More recently, Prigent et al²⁶ have explored the possibility of sizing both transmural and nontransmural myocar-

dial perfusion defects using gated Tc-99m sestamibi myocardial perfusion SPECT imaging in the experimental dog model. SPECT imaging was performed over 180° using a 128 × 128 matrix, high-resolution collimator and 64 projections. Acquisition was gated to obtain 8 frames/ R-R interval. The 3 diastolic frames were isolated and summed into a single diastolic projection image for each of the 64 projections. For quantitation of defect size on individual slices, the previously described approach for Tl-20127,28 was improved by defining defect size as the pixel area enclosed between the experimental profile and a given threshold, divided by the entire pixel area below the threshold. The threshold giving the best correlation between the TTC infarct size and the SPECT infarct size in a sample of 6 "calibration" slices was used for determining infarct size on the remaining slices. There was a high correlation between the Tc-99m sestamibi and the pathologic infarct size in 16 slices with transmural infarction (Fig. 8), with a correlation coefficient of 0.90 and a concordance correlation coefficient of 0.88, the latter expressing the 1-to-1 relation between the measurements. For the remaining slices that had nontransmural infarction (n = 15) or were normal (n = 2), the correlation coefficient was 0.89 (Fig. 9), and the concordance correlation coefficient was 0.88. The findings suggest that Tc-99m sestamibi SPECT will prove accurate for the volumetric quantitation of the extent of hypoperfused myocardium.

ABSOLUTE QUANTIFICATION OF MYOCARDIAL PERFUSION

A major problem with Tl-201 and Tc-99m sestamibi SPECT studies is variable attenuation caused by varying distance of myocardial regions from the collimator and variable thickness of tissues interposed between the myocardium and the collimator. These attenuation patterns

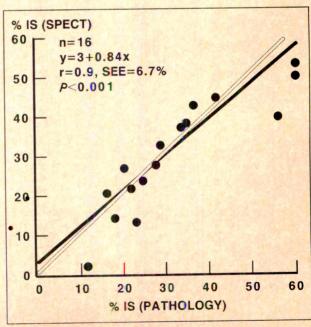


FIGURE 8. Plots of the relation between quantitative tomographic and pathologic transmural infarct size (IS) (see text).

are frequently the source of false-positive studies. In a collaborative study between Emory University and Cedars-Sinai Medical Center, various algorithms that are aimed at correcting for attenuation and scatter are being developed and validated through studies on phantom and experimental animals.²⁹ Attenuation correction is accomplished by first obtaining a transmission map of the heart and surrounding structures. An attenuation correction matrix is then generated from this transmission map, and this matrix is applied to the raw data before reconstruction using the first order Chang correction method.²⁹ This approach may ultimately add 10 minutes to the acquisition time and another 10 minutes to the processing time. For scatter correction, myocardial images are obtained on 2 different photopeaks simultaneously with the photopeak of 106 keV yielding a scatter image that is then used to correct the 140 keV "on peak" study (Fig. 10). Application of scatter and attenuation correction as well as correction for object size may make it feasible to obtain absolute measurement of regional myocardial counts. Incorporation of this technique may ultimately result in an improvement in the diagnostic accuracy for detection of coronary artery disease.

FUTURE DIRECTIONS

To exploit the high count rates and other physical and biological properties of Tc-99m sestamibi, future directions in the development of Tc-99m sestamibi SPECT encompass several important research projects.

Development of optimal parameters for single photon emission computed tomography acquisition and processing: Important preliminary evidence suggests that further improvement in Tc-99m sestamibi SPECT image quality is likely to evolve when protocols are specifically tailored to the physical and biological characteristics of this new agent. Recently a collaborative study

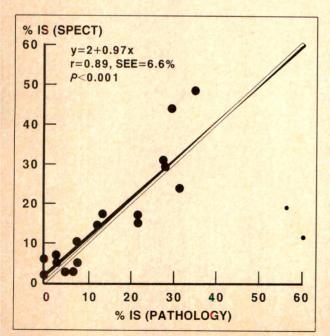


FIGURE 9. Plots of relation between quantitative tomographic and pathologic nontransmural infarct size (IS) (see text).

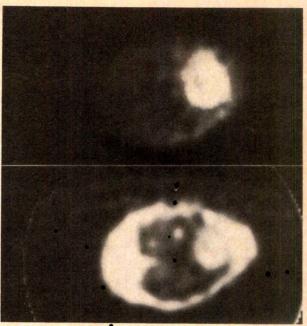


FIGURE 10. Attenuation (top) and scatter (bottom) tomograms at the midlevel of the canine myocardium. The attenuation tomogram was generated from transmission projection data. The brightness of the anatomic structures reflects the degree of attenuation. From these tomograms an attenuation correction matrix can be generated and applied to prospective data. The scatter tomogram was generated from projection data acquired at the 106 keV photopeak.

between Cedars-Sinai Medical Center and Emory University was designed to optimize acquisition and processing. 30,31 Parameters for Tc-99m sestamibi SPECT acquisition were evaluated using a realistic phantom that mimicked the myocardium, myocardial perfusion defect, lung and spine with count rates simulating those encountered in clinical settings. Comparison of various combinations of SPECT acquisition and processing parameters showed that, compared to the all-purpose collimator and 64 × 64 matrix combination previously shown to be optimal for Tl-201, a 128 × 128 matrix and high-resolution collimator combination significantly improved the defect contrast and the definition of endocardial and epicardial borders in phantoms. This improvement appears to be predominantly due to the use of a high-resolution collimator. Subsequent clinical application of the parameters at Cedars-Sinai Medical Center and Emory University have indicated that to maintain acceptable uniformity in the tomograms and reduce disk requirements, a 64 × 64 matrix is preferred over the 128 × 128 matrix. An optimized low-dose-high-dose, rest-stress same-day protocol that demonstrates excellent image quality is currently being evaluated by our centers. These optimization steps are described in greater detail by Garcia et al in this supplement.32

Gated single photon emission computed tomography acquisition: Due to high count rates, Tc-99m sestamibi images can be acquired with cardiac gating. Kahn et al³ have demonstrated that analysis of regional wall motion on gated SPECT studies allows differentiation of viable and nonviable myocardial regions. In areas of reduced

Tc-99m sestamibi activity, viable myocardial regions demonstrated regional wall motion while nonviable myocardial regions had a lack of motion. Analysis of diastolic Tc-99m sestamibi SPECT studies may improve the ability to detect small perfusion defects and thereby improve the threshold for detection of myocardial perfusion abnormalities. In addition, viewing gated Tc-99m sestamibi data in a cine format should offer an additional quality control method for identification of SPECT imaging artifacts (i.e., breast and diaphragm artifacts).

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Clinical Experience with Technetium-99m Teboroxime, a Neutral, Lipophilic Myocardial Perfusion Imaging Agent

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Technetium-99m (Tc-99m) teboroxime is a new technetium-based myocardial perfusion imaging agent (investigational code = SQ30217 [Cardiotec, Squibb Diagnostics]). A member of a class of neutral, lipophilic, technetium-containing complexes known as boronic acid adducts of technetium dioxime (BATO) complexes, this agent is chemically very different from the cationic tracer thallium-201 (TI-201) and from the cationic technetium complex Tc-99m sestamibi (Cardiolite, Du Pont Imaging Agents). Tc-99m teboroxime has high myocardial extraction, rapid blood clearance, little lung uptake and rapid myocardial washout. A biexponential pattern of myocardial washout is demonstrated in animals and in man. Effective half-lives of the 2 washout components in man are 5.2 minutes and 3.8 hours and represent approximately 66 and 33% of the myocardial activity, respectively. The first half-life for the myocardium is approximately 11 minutes. As the agent washes out of the heart, hepatic uptake occurs, peaking at about 5 minutes after injection. The liver is the major organ of excretion and receives, along with the large bowel, the largest radiation dose. Rapid imaging protocols using standard cameras have achieved good myocardial counts from 3 planar views acquired over a 4- to 5-minute period or for single photon emission computed tomography (SPECT) images acquired over a 10-minute period. An entire stress/rest procedure can be completed in 1 hour. Analysis of data from 155 patients from 4 centers using planar or SPECT imaging showed a sensitivity and specificity for blinded readings of 82 and 91%, respectively, when compared against overall clinical impression. There was a high agreement between blinded readings of Tc-99m teboroxime and Tl-201 scans from the same patient (90%). Studies in progress include measurement of regional myocardial washout from dynamic SPECT acquisitions performed with a 3-headed SPECT camera, and combined function and perfusion tests using a portable high count rate camera.

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lthough myocardial perfusion imaging with thallium-201 (Tl-201) has become a mainstay in the diagnosis and management of coronary artery disease (CAD), Tl-201 is not an ideal imaging agent, especially when compared with technetium-99m (Tc-99m). Two new technetium-based myocardial perfusion imaging agents, Tc-99m sestamibi and Tc-99m teboroxime, have recently been developed, and both have undergone clinical trials. 1-3 Tc-99m teboroxime is in a class of neutral, lipophilic, technetium-containing complexes known as boronic acid adducts of technetium dioxime (BATO) complexes. The pharmacokinetics of Tc-99m teboroxime are very different from those of the cationic tracer Tl-201 or the cationic technetium complex Tc-99m sestamibi. Tc-99m teboroxime has high myocardial extraction and rapid myocardial washout. It has shown promise as a myocardial perfusion imaging agent used with stress testing. The rapid myocardial washout necessitates brief imaging protocols.

PHARMACOKINETICS AND PREPARATION

Tc-99m teboroxime is produced by template synthesis when Tc-99m is added to a vial containing the appropriate vicinal dioxime, methyl boronic acid, and the vial is heated at 100°C for 15 minutes. The chemical structure is shown in Figure 1. Tc-99m teboroxime is supplied in kit form as a lyophilized powder in sterile evacuated vials. Up to 100 mCi of Tc-99m in 1 ml of 0.9% sodium chloride is added to the contents of the vial. The vial is placed in a 100°C water bath for 15 minutes, and then allowed to cool. Two doses of 15 mCi each (rest and stress) can be obtained from the same vial. The presence of saline soluble contaminants and reduced technetium species is monitored with paper chromatography. One drop of the preparation is placed on each of two 1.3 cm × 11 cm Whatman 31 ET strips. One strip is developed in normal saline while the other is developed in a 50:50 (by volume) normal saline/acetone solution. The criterion for injection, which was met in all the phase II and III clinical trials, is that the sum of saline soluble contaminants and reduced technetium species be <10%.

A high myocardial uptake of Tc-99m teboroxime (3.44% injected dose) was demonstrated in experimental animals.⁴ The clearance of Tc-99m teboroxime from the blood is biexponential. The first half-life time is 0.79 minutes (88%); the second half-life time is 154 minutes (12%). Early planar imaging studies in man showed little lung uptake. Leppo and Meerdink⁵ have used an isolated blood perfused rabbit heart preparation and indicator dilution techniques to evaluate cardiac transport of perfu-

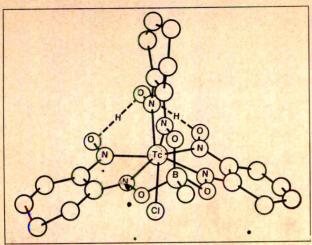


FIGURE 1. Chemical structure of technetium-99m teboroxime, a member of the chemical group called boronic acid adducts of technetium dioxime complexes. B = boron; Cl = chlorine; H = hydrogen; N = nitrogen; O = oxygen; Tc = technetium.

sion agents. These investigators found higher values for mean fractional extraction (measured over a range of flows) and for capillary permeability surface area product for Tc-99m teboroxime than for Tl-201 or Tc-99m sestamibi.⁵ Although Tc-99m teboroxime has high extraction and initial capillary permeation, it has a rapid myocardial washout. Thus, net extraction values, which combine the summation of tracer washin and washout, were not as different among the three.

A biexponential pattern of myocardial washout is demonstrated in animals⁴ and in humans. Myocardial washout data in humans were collected from phase I studies performed at Duke University (unpublished data). Washout data from each individual patient were fitted to a biexponential curve, and the curves were combined using Systat software (Fig. 2). Effective half-lives of the 2 washout components in humans are 5.2 minutes and 3.8 hours and represent approximately 66 and 33% of

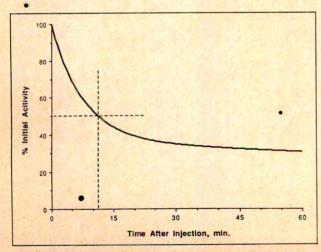


FIGURE 2. Myocardial washout of technetium-99m teboroxime. The first half-life of the myocardium is approximately 11 minutes.

the myocardial activity, respectively. Thus, the first halflife for the myocardium is approximately 11 minutes. At 1 hour after injection, about 30% of the initial myocardial activity remains in the myocardium. However, with standard planar imaging, no detectabled activity is present over the heart (Leppo et al, unpublished data). Single photon emission computed tomography (SPECT) imaging at 1 hour does show some myocardial activity. As the agent washes out of the heart, hepatic uptake occurs. Hepatic uptake peaks between 4.5 and 7.0 minutes after injection.6 The liver is the major organ of excretion and is, along with the large bowel, the target organ for dosimetry. The liver receives 3.6 rads and the upper tract of the large intestine 3.3 rads from 2 (rest and stress) 15-mCi doses of Tc-99m teboroxime. The total body dose is 510 mrads. This compares with a total body dose of 630 mrads from a 3-mCi dose of Tl-201.

IMAGING PROTOCOLS AND CLINICAL TRIALS

Tc-99m teboroxime's rapid myocardial washout necessitates rapid imaging protocols. There are theoretical limitations to performing standard SPECT imaging when tracer activity within the field of view varies significantly during the SPECT acquisition. Under these circumstances, projection images would be unequally weighted in the reconstruction procedure, potentially producing artifacts. Bok et al7 performed a phantom experiment addressing this question. By simulating time dependence of the tracer concentration, these investigators found that when the activity imaged follows a decaying exponential function, a distortion factor may be defined as the ratio of the total imaging time divided by the tracer half-life in the object imaged. They found that a change in activity of less than a factor of 2 results in little image distortion. Since the first half-life of Tc-99m teboroxime in the myocardium is approximately 11 minutes, and standard SPECT acquisitions, beginning within 2 minutes of Tc-99m teboroxime injection, can be completed in 10 minutes, there may be little image distortion from varying tracer activity.

The first study using Tc-99m teboroxime and planar imaging in control subjects and coronary disease patients was performed by Seldin et al3 (Table I), who used upright bicycle exercise with the patient positioned in front of an Anger camera (Picker Dynamo, Picker International) to allow imaging as soon as blood pool activity cleared (about 2 minutes). Three standard planar views were acquired for 3, 5, and 6 minutes, respectively (Fig. 3), beginning with the anterior projection to allow visualization of the inferior wall before hepatic uptake occurred. Stress imaging was performed first, followed 2 hours later with a rest injection. A 15-mCi dose of Tc-99m teboroxime was used for each injection. Thirty subjects-10 normal volunteers and 20 patients with CAD documented by recent angiography—all had stress perfusion imaging performed with both Tl-201 and Tc-99m teboroxime. There was no significant difference between the 2 techniques for identifying abnormal vessels (Tc-99m teboroxime, 19 of 45; Tl-201, 21 of 45) or detecting CAD (Tc-

TABLE I Studies Using Technetium-99m and Planar Imaging

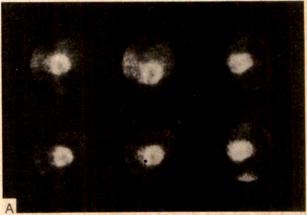
Investigator	No.	Туре	Camera/ Window	Time (First Image)	Total Imaging Time	Counts/FOV (First Image)	Technical Factors
Seldin and Johnson	31	Planar 20%	SFOV	3 minutes	20 minutes	700K	Liver third view
Leppo	30	Planar 15%	LFOV	60 seconds	4–5 minutes	300-400K	Liver third view
Bellinger	20	Planar	LFOV	60 seconds	4–5 minutes	350K	Liver third view
	40	SPECT	Single head 20%		10 minutes		Liver seen
Drane	20	Planar	LFOV	3 minutes	20 minutes		Liver third view
	15	SPECT	Single head		10 minutes		Liver uptake
	15	SPECT	Triad 20%		2 minutes		No liver
Seldin and Johnson	5	Planar	Scinticor SIM-400	60 seconds	4–5 minutes	800K	Also EF data ? resolution
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All imaging was begun within 2 minutes of injection. Dose of 15 mCi used in all stress injections.

EF = ejection fraction; FOV = field of view; L = large; S = small; SPECT = single photon emission computed tomography; ? = questionable.

99m teboroxime, 16 of 20; Tl-201, 17 of 20). However, significantly more defects were identified as fixed on resting Tc-99m teboroxime scans than on Tl-201 redistribution scans. This might be due to residual background myocardial activity from the first (exercise) injection. Similar observations have been made with Tc-99m sestamibi on same-day stress-rest studies when second-injection rest scans were compared to Tl-201 redistribution scans.8 Hepatic uptake of Tc-99m teboroxime, which was apparent in the second image (shallow left anterior oblique) in all subjects, obscured inferoapical segment analysis in 14 of 20 patients but did not interfere with abnormal vessel identification. Seldin et al3 were restricted to an imaging protocol lasting about 20 minutes, which included camera repositioning time. Subsequently, it was shown independently by Leppo and by Bellinger that adequate myocardial counts can be acquired by an Anger camera in 40 to 60 seconds/view after Tc-99m teboroxime injection (personal communication). These investigators showed that using large field-of-view (LFOV) detectors, counts per image ranged from 300,000 to 400,000 (Fig. 4). Both of these investigators used planar imaging protocols that were completed within 4 to 5 minutes. Standard SPECT imaging using single-head cameras and 10-minute acquisitions over 180° using standard "stop and shoot" software was performed by several groups of investigators (Table I). Continuous acquisition of counts over 180° shortens the total acquisition time to under 6 minutes, minimizing the effects of hepatic uptake

The planar and SPECT data from 4 groups of investigators participating in the phase III trial were combined for analysis.9 The "gold standard" in this trial was identified as "overall clinical impression," which was defined as the results of all clinical data except for the Tc-99m teboroxime data and included angiography plus Tl-201 in 61 patients, angiography alone in 40 and Tl-201 alone in 54. For the 101 patients who had coronary angiography plus Tc-99m teboroxime study, the agreement for detect-



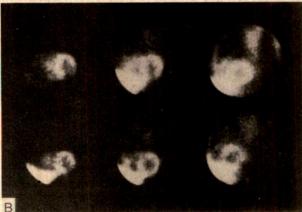


FIGURE 3. A, Thallium-201 exercise (top) and redistribution (bottom) images in the anterior, 30° left anterior oblique and 60° left anterior oblique views in a patient with 99% stenosis of the left anterior descending coronary artery. There is decreased perfusion of the anteroseptum and apex with partial redistribution at 4 hours. B, Technetium-99m teboroxime exercise (top) and rest (bottom) images of the same patient showing a comparable anteroapical defect, which partially fills in on reinjection. Hepatic activity on the steep oblique view obscures the inferoapical segment on the exercise image and the anteroapical and inferoapical segments on the rest image. (Reproduced with permission from J Nucl Med.3)

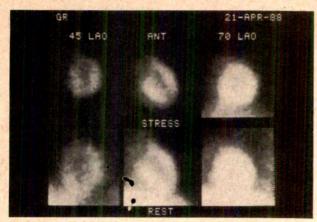


FIGURE 4. Technetium-99m teboroxime exercise (top) and rest (bottom) planar images acquired with rapid imaging sequence (40 seconds/image) on large field-of-view camera showing prominent apical cleft. Coronary angiography showed insignificant coronary artery disease. Study performed by Ray Bellinger, MD, Travis Air Force Base, California. ANT = anterior; LAO = left anterior oblique.

ing CAD was 76% and was not different from the agreement between coronary angiography and Tl-201 scintigraphy (80%). For the 115 patients who underwent Tc-99m teboroxime and Tl-201 scintigraphy, the agreement between the 2 imaging modalities was 90%. The overall sensitivity and specificity for blinded reading were 82 and 91%, respectively, when compared against overall clinical impression.

STUDIES IN PROGRESS

Because of the unique pharmacokinetic properties of Tc-99m teboroxime, several clinical applications are being pursued that take the aforementioned standard imaging protocols 1 step further. Tc-99m teboroxime is a neutral, lipophilic agent with rapid myocardial washout. The removal rate of a neutral lipophilic agent that freely enters and leaves a myocardial cell should be related to capillary blood flow. Tc-99m teboroxime thus bears similafities to xenon-133, the inert gas that was injected into the coronary arteries to quantitate regional myocardial blood flow from initial washout using the Schmidt-Kety formula and a multicrystal scintillation camera. 10 Differences in regional Tc-99m teboroxime washout may be used to estimate regional differences in myocardial blood flow. To overcome curve contamination by residual blood pool activity and overlap of coronary vascular beds in any single planar projection, SPECT acquisition is preferable for this application. Drane and co-workers 11 are performing dynamic SPECT imaging with Tc-99m teboroxime and a 3-headed SPECT camera. These investigators acquire ten 2-minute sequential SPECT acquisitions. In addition to measuring regional washout, they compare the initial scans to normalized scans acquired at 18 to 20 minutes after injection to determine redistribution. This redistribution is actually differential washout due to the slower clearing of activity from myocardium in the distribution of stenosed arteries compared to clearance from

myocardium in the distribution of normal arteries. Their initial results suggest that abnormal washout in the distribution of stenosed vessels can be detected after a single Tc-99m teboroxime injection with dynamic SPECT imaging using a 3-headed SPECT camera.11

The rapid bolus injection of Tc-99m pertechnetate and a multicrystal scintillation camera have been the major components of the first-pass technique for measurement of left and right ventricular ejection fractions. There is an extensive collection of published studies that apply this technique to rest and bicycle exercise studies in patients with valvular disease and CAD. The best data supporting the clinical usefulness of exercise first-pass scintigraphy comes from the Duke database and the work of Robert Jones. These investigators found that the exercise left ventricular ejection fraction was the most important single independent predictor of mortality in coronary disease.¹² A newer model of a high count rate, portable multicrystal scintillation camera is now available (SIM-400, Scinticor). This camera, which has a very small field of view, can be used with treadmill exercise. Johnson, Seldin and co-workers developed a protocol using Tc-99m teboroxime and the portable high count rate camera equipped with a 1-inch collimator to maximize resolution and a motion correction program developed by Port and colleagues. 13 Before exercise, a low-energy radioactive source is fastened on the skin over the sternum. The patient runs on the treadmill with the chest positioned several inches in front of the camera detector and is injected with 15 mCi of Tc-99m teboroxime as a bolus at peak exercise. Dynamic dual isotope imaging is acquired for 50 seconds, the treadmill is slowed and the patient is seated next to the treadmill. Three planar images using only the technetium window are acquired within 4 minutes. The low-energy source is used to correct the dynamic first-pass data for patient motion. The potential draw-

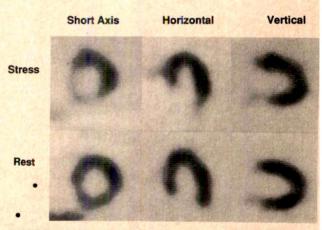


FIGURE 5. Technetium-99m teboroxime stress (top) and rest (bottom) single photon emission computed tomography reconstructions acquired as a 6-minute 180° rotation on standard single-head rotating gamma camera. Anteroseptal and inferobasal defects show almost complete fill-in on resting scans. Study performed by David Yuille, St Luke's Medical Center, Milwaukee, Wisconsin.

back to this technique is the limited resolution of the high count rate camera (equivalent to a 40 × 40 matrix on an SFOV Anger camera) (Fig. 6). Small defects may be missed, but this deficit may be balanced by the additional diagnostic information added by the left ventricular ejection fraction numbers. The entire stress and rest procedure with 2 sets of planar images and ventricular functional data can be obtained within 1 hour.

SUMMARY

Tc-99m teboroxime is a technetium-based myocardial perfusion imaging agent. It is one of the BATO compounds, which are neutral and lipophilic. Its pharmacokinetics are very different from those of Tc-99m sestamibi. a cationic technetium-based myocardial perfusion agent. The myocardial extraction for Tc-99m sestamibi is less than that for Tl-201, whereas the myocardial extraction for Tc-99m teboroxime is greater than that for Tl-201. Tc-99m sestamibi has very slow myocardial washout and negligible redistribution, whereas Tc-99m teboroxime has rapid myocardial washout, with differential washout rates in the distribution of stenotic and normal vessels, leading to apparent "redistribution" soon after injection. The first half-life for the myocardium is 11 minutes. As Tc-99m teboroxime is washing out of the heart, hepatic uptake occurs, peaking at 4.5 to 7.0 minutes. The combination of rapid myocardial washout and early hepatic uptake has necessitated developing rapid imaging protocols. Protocols using standard Anger cameras and 40- to 60-second planar acquisitions or 180° rotational SPECT and 10-minute acquisitions beginning within 2 minutes of injection have minimized interference from hepatic uptake, while yielding high counts over the myocardium. The sensitivity and specificity for detecting CAD or identifying abnormal vessels are comparable to those with Tl-201. Stress and rest studies can be performed within 1 hour. Although good images can be acquired using standard cameras, cameras with rapid counting or imaging capabilities are uniquely suited for this agent. A 3-headed

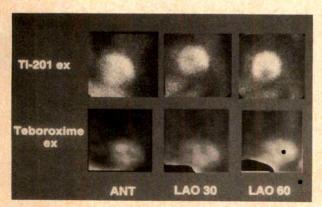


FIGURE 6. Exercise thallium-201 (TI-201) planar images (top) and technetium-99m teboroxime planar images (bottom) showing posterolateral defect in a patient with an old posterolateral infarct. Acquired with rapid imaging sequence (30 seconds/image) on SIM-400 multicrystal camera. ANT = anterior; LAO = left anterior oblique; ex = exercise.

SPECT camera with rapid acquisition and the Scinticor SIM-400, a portable high count rate camera, are well suited to imaging Tc-99m teboroxime. The SIM-400 gives ejection fraction data as well as perfusion imaging, but the image quality of the latter may be limited by the poorer resolution of a multicrystal camera.

Although both Tc-99m sestamibi and Tc-99m teboroxime will probably compete with each other and with Tl-201 in stress/rest (redistribution) perfusion imaging, the very different pharmacokinetics of the 2 technetium perfusion imaging agents present a definite choice to nuclear imaging laboratories. A complete diagnostic study including stress and rest ejection fraction performed in 1 hour, compared to 5 hours for Tl-201 stress and redistribution, will probably find high patient approval. Laboratories must, however, be set up for rapid patient movement between treadmill and camera. Alternatively, pharmacologic stress with intravenous dipyridamele or adenosine can be administered while the patient is lying under the camera, obviating the need to move the patient and potentially shortening pharmacologic stress/perfusion imaging studies. Both Tc-99m teboroxime and Tc-99m sestamibi offer the opportunity to acquire function and regional perfusion data in a single procedure, which will add important diagnostic and prognostic information to the study

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Simultaneous Measurement of Myocardial **Perfusion and Ventricular Function During Exercise from a Single Injection of Technetium-**99m Sestamibi in Coronary Artery Disease

Robert H. Jones, MD, Salvador Borges-Neto, MD, and Jonathan M. Potts, MD

New radiopharmaceuticals permit simultaneous assessment of myocardial perfusion and left ventricular function using a single tracer injection. The purpose of this study was to quantitate the relation between myocardial perfusion and function at rest and during exercise in patients with documented coronary artery disease (CAD). A rest first-pass radionuclide angiocardiogram (RNA) was recorded in 51 patients with CAD during injection of 10 mCi of technetium-99m (Tc-99m) sestamibi, and tomographic perfusion images were obtained 60 minutes later. A treadmill test was then performed, and on attainment of an exercise end point a second first-pass RNA was recorded with 30 mCi of Tc-99m sestamibi. Tomographic images reflecting myocardial perfusion during exercise were obtained 1 hour later. Tomographic perfusion defect size, quantified using modifications of the Cedars-Sinai program, correlated directly with end-systolic volume and inversely with ejection fraction at rest and during exercise. However, perfusion defect size often varied widely in patients with similar left ventricular function. This independence between measurements of perfusion and function suggests that simultaneous assessment of the 2 physiologic variables could improve the diagnostic and prognostic information of radionuclide tests.

(Am J Cardiol 1990;66:68E-71E)

rior studies have documented radionuclide measurement of myocardial perfusion and left ventricular function to be useful for determining prognosis in patients with coronary artery disease (CAD).1 The development of technetium-99m (Tc-99m)-labeled radiopharmaceuticals with high myocardial extraction permits simultaneous measurement of myocardial perfusion and left ventricular function (as well as exercise electrocardiography) during a single period of exercise.2 This approach to evaluation of patients with CAD, which provides information equivalent to that formerly requiring 2 separate studies, facilitates assessment of the independence and relative importance of electrocardiographic, myocardial perfusion and left ventricular function variables. The purpose of this investigation was to document the degree of concordance of global measurements of myocardial perfusion and left ventricular function using a single injection of Tc-99m sestamibi during treadmill exercise in patients with CAD.

METHODS

Study population: We prospectively studied 51 patients with documented CAD. These 40 men and 11 women had a mean age of 59 years (range 35 to 77). Percutaneous transluminal coronary angioplasty had been performed 6 months earlier in 45 patients, and 1 patient had undergone coronary artery bypass grafting. Coronary angiography was performed within 3 months of the study in all but 1 patient. Cardiac medication taken at the time of the radionuclide angiocardiogram (RNA) included calcium antagonists in 39 patients, nitrates in 12 patients, β-adrenergic blockers in 5 patients and digitalis in 2 patients. Myocardial infarction defined by typical pain associated with evolutionary electrocardiographic and enzymatic abnormality (creatine kinase-MB >12) had been documented at some time before study in 32 of the 51 patients. The heterogeneous composition of the study population permitted evaluation of the relation of myocardial perfusion and left ventricular function over a wide spectrum of severity of ischemic manifestations of coronary artery disease.

Study plan: A rest first-pass RNA was recorded using a bolus injection of 10 mCi of Tc-99m sestamibi. Single photon emission computed tomographic (SPECT) images were obtained with patients supine 1 hour later. Subsequently, patients performed treadmill exercise using the Bruce protocol. When patients attained an exercise end point (85% of age-predicted maximal heart rate,

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severe fatigue, angina, arrhythmias or dysfunction), a treadmill exercise first-pass RNA was recorded using a rapid bolus injection of 30 mCi of Tc-99m sestamibi. Exercise was terminated 1 minute after injection, and SPECT imaging began 1 hour after the second injection. The total rest and exercise evaluation was completed within a single 4-hour interval.

Radionuclide angiocardiogram: RNAs were acquired in the anterior projection at 20-ms intervals using a portable multicrystal gamma camera (Scinticor, Inc.). The total acquisition time was 24 seconds. Data from 20 × 20 count matrices were processed to yield standard descriptors of left ventricular function using commercial software similar to that developed and validated at this institution.3 The histogram of left ventricular counts as a function of time was used to identify times of end diastole and end systole of all cardiac cycles for which count activity was at least 70% of that of the maximum beat. Data from beats selected for processing (range 4 to 10 beats) were compiled into a single representative cardiac cycle. Left ventricular ejection fraction was calculated from the counts change of the background-corrected representative cycle. The left ventricular end-diastolic volume was calculated by the area-length method of Dodge et al.4 The count-derived ejection fraction and imagederived end-diastolic volume were used to calculate the stroke volume and end-systolic volume.

Motion correction was performed as follows: movement of a low-energy 8-mCi I-125 point source affixed to the skin was used to track chest motion in each frame of data. Computer repositioning of data frames so that the point source was fixed eliminated blurring of cardiac images due to patient motion during exercise. This approach made treadmill exercise feasible, and the results of the treadmill examination could be reported in concert with those of the myocardial scintigram and RNA.

Single photon emission computed tomography studies: Perfusion imaging was performed using a rotating gamma camera (Siemens Orbiter) fitted with a low-energy, all-purpose collimator and interfaced to a computer (Medasys Paragon). SPECT acquisition was performed with a 15% energy window using 64 imaging stops of 30 seconds duration through a 180° arc from the 45° right anterior oblique to the 45° left posterior oblique position. Images were stored on a floppy disk in a 64 × 64 matrix for subsequent analysis. Prefiltered images were transaxially reconstructed using a standard back-projection technique with a Butterworth filter (order 5 and 20% cutoff). Correction for field nonuniformities and center of rotation was applied. Reconstructed tomographic slices with 6-mm thickness were reoriented in the short and vertical long axes and displayed on a color monitor for visual interpretation.

Computer quantification of perfusion defect: Tc-99m sestamibi tomograms were quantified using modification of the Cedars-Sinai computerized 2-dimensional polar maps.⁵ Slices for quantification were selected as described for the Cedars-Sinai thallium-201 SPECT method.⁶ The center of the left ventricle and alignment points were defined from the short- and vertical long-axis slices.

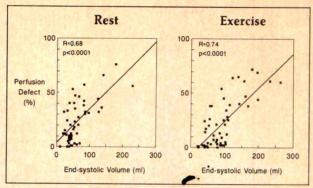


FIGURE 1. Comparison of end-systolic volume at rest and exercise with percent of myocardium with perfusion defect by single photon emission computed tomography.

The distribution of radioactivity was determined for each tomographic slice using a circumferential profile technique. The pixel with the highest count over each radius was plotted, and the normalized short-axis circumferential profiles were then color-coded and displayed as concentric rings from cardiac apex to base. Apical count profiles were derived from the vertical long-axis slices. The resulting quantitative polar maps from each rest and exercise study of each patient were compared with rest and exercise polar maps obtained from 23 normal subjects who met criteria for a \$5\% likelihood of having CAD, exclusive of the results of the scintigraphic variables.² Any region on a patient study with counts below those observed in the corresponding region in any of the normal subject studies was defined as a perfusion defect. The percent of the total regions within the polar map with perfusion less than normal was defined as the total perfusion defect of the left ventricle. The percent perfusion defect was correlated to the end-systolic volume and ejection fraction by least square regression analysis.

RESULTS

Electrocardiographic, perfusion and function data of good quality were obtained at rest and exercise within a 4-hour total study interval in all patients. The percent of the left ventricle involved with some perfusion defect ranged from 0 to 76% at rest and from 0 to 72% during exercise. Therefore, the population studied provided a full spectrum of patients with ischemia and infarction to compare the relation between perfusion and function. End-systolic volume and ejection fraction are the 2 descriptors of global left ventricular function obtained by RNA that relate best to the contractile state of the heart. Therefore, these variables measured at rest and exercise were correlated to the percent of the ventricle demonstrating a perfusion defect on quantitative SPECT images.

In the group of 51 patients, the resting end-systolic volume ranged from 11 to 229 ml, and the exercise end-systolic volume ranged from 21 to 263 ml. A linear correlation was observed between the end-systolic volume and the percent perfusion defect both at rest and during exercise (Fig. 1). Patients with the largest end-systolic volumes were those with the greatest percent of the ventricle

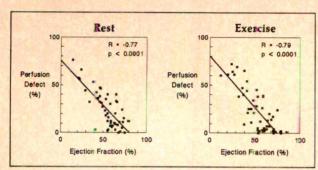


FIGURE 2. Comparison of left ventricular ejection fraction at rest and exercise with percent of myocardium with perfusion defect by single photon emission computed tomography.

demonstrating decreased perfusion. The resting ejection fraction ranged from 0.14 to 0.85, and exercise ejection fraction ranged from 0.12 to 0.85. The ejection fraction on both studies correlated inversely with the total perfusion defect (Fig. 2). All but 1 patient with resting ejection fractions <0.50 had a rest perfusion defect involving at least 20% of the myocardium.

Individual data illustrate the range of perfusion defects apparent among patients with similar exercise left ventricular function (Fig. 3). In these 6 patients, the exercise left ventricular ejection fraction ranged from 0.46 to 0.54, which is within the range of reproducibility of this measurement. However, the percent of myocardium involved with a perfusion defect ranged from 0 to 38% in these 6 patients.

DISCUSSION

Radionuclide techniques measuring ventricular function and myocardial perfusion reflect similar biologic processes because of the close link between myocardial integrity and blood flow. Myocardial infarction with subsequent fibrosis decreases resting left ventricular function and results in a resting perfusion defect because of loss of myocardial mass and the lower tissue blood flow to fibrotic myocardium. Although myocardial ischemia may occur silently and at rest, it is most consistently evoked by increased myocardial work during exercise. The appearance of worsening perfusion defects on myocardial scintigraphy, or the development of regional or global dysfunction on RNA, reflects myocardial ischemia.

Measurements of both myocardial perfusion and left ventricular function have been shown to relate to prognosis in patients with CAD. Myocardial scintigraphic variables that provide the greatest prognostic information are those that reflect both the extent and severity of perfusion abnormalities.7 In more than 2,000 patients at Duke University Medical Center followed for up to 10 years after RNA, the exercise ejection fraction was the single most important descriptor of left ventricular function relating to prognosis.8 This single variable contained more prognostic information than any cardiac catheterization variable and accounted for 80% of the prognostic information of the radionuclide study. An exercise ejection fraction ≥0.50 was associated with a low incidence of cardiac event or death.

Prognostic evaluation has not been reported in a lar series of patients assessed by both myocardial scintigr phy and measurements of cardiac function. A degree redundancy of information is assured by the demo strated correlation between perfusion and function. The variables are interrelated but not identical, and diffe ences might provide independent prognostic informatic Myocardial scintigraphy excels in defining the relati distribution but not the total myocardial flow. Therefor localized severe blood flow depression causes a more a parent perfusion test abnormality than the same tot flow deficit spread diffusely throughout the left ventric especially in concert with scattered myocardial fibros In contrast, the severity of global left ventricular dysfun tion during exercise appears to relate to the total magr tude of ischemic and fibrotic impairment of the ventric with minimal differentiation between the 2 abnorma ties. The degree to which differences observed in me surements of myocardial perfusion and left ventricula function in an individual patient might aid clinical maagement has remained an important question. The intr duction of Tc-99m sestamibi now makes feasible simult neous assessment of myocardial perfusion and left ver tricular function. The purpose of the present study was

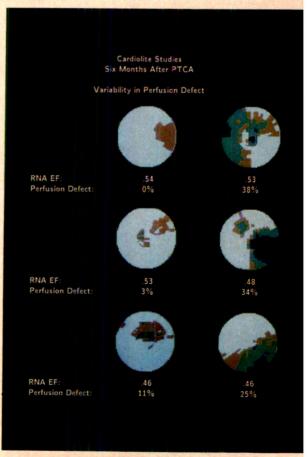


FIGURE 3. Individual tomographic polar map images in 6 patients with similar left ventricular ejection fractions. EF = ejec tion fraction; PTCA = percutaneous transluminal coronary angioplasty; RNA = radionuclide angiocardiogram.

use this new technology to define the range of difference and agreement between these 2 variables.

First-pass RNA was used to measure left ventricular function during Tc-99m sestamibi injection. A multicrystal gamma camera provided an adequate count rate to permit the 2 injections necessary for a rest and exercise determination of ejection fraction on the same day. The count rate capability of the most sensitive single crystal camera is about 50% that of the multicrystal camera. To perform rest and exercise studies of adequate data density using single crystal cameras, a larger amount of radioactivity is required than with the multiple crystal camera. This results in a larger radiation dose for the patient and is not likely to allow performance of rest and exercise studies on the same day. 9 A same-day protocol performed using 10 mCi of Tc-99m sestamibi for the rest study and 30 mCi for the exercise study represents an important logistic advantage in many clinical situations. An added advantage of the Scinticor multicrystal camera is that simultaneous dual energy acquisition permits correction of data for patient motion during exercise. Therefore, a single study period requiring <4 hours results in simultaneous measurements of the electrocardiogram and myocardial perfusion and function at rest and during exercise.

Results of the present study define a strong group relation between measurements of perfusion defect and global left ventricular function. The quantitative Cedars-Sinai SPECT algorithm used in this study indexes the extent of perfusion defect as a percent of the left ventricular image. However, the current program does not permit assessment of the severity of this abnormality. Moreover, this software does not quantify much of the base of the heart because of difficulties in adjustment for variable attenuation in this region. Elimination of regions at the base of the heart artificially elevates the calculated percent of perfusion defect relative to the actual left ventricle. Despite these approximations and limitations, this single perfusion variable related well to the ejection fraction and end-systolic volume measurements both at rest and during exercise. This relation documents the expected interdependence of myocardial perfusion and function and provides credibility for the two approaches of measurement. Although this relationship is encouraging, the assessment of left ventricular ejection fraction during treadmill exercise is new, and its accuracy requires further validation.

Agreement within the entire group appeared strongest in the midranges of abnormalities. However, sufficient individual variation was apparent to justify further investigation to document the relative diagnostic and prognos-

tic information reflected by these observed differences. Patients with near-normal perfusion and function and those with severe abnormalities tend to show more discrepancies between individual measurements of perfusion and function. It seems reasonable to assume that patients with normal assessments by all test variables can be regarded as having minimal or no CAD. Patients with severe exercise-induced abnormalities on both perfusion and function tests would be those with very severe disease, and these results might indicate potential benefit from interventional therapy. However, discrepancies in abnormalities in perfusion and function might also aid patient management. For example, patients with an exercise left ventricular ejection fraction of 0.00 are known to be in a gray zone as far as management is concerned. These patients potentially can be treated as safely on a medical regimen as by interventional therapy. Further observations in this subgroup of patients may identify which specific treatment leads to better clinical results.

Results of this investigation suggest that it will be important to document the amount of variability between measurement of perfusion and function due to inaccuracy of methodology, as well as that which represents differences in biologic processes in individual patients. More precise definition of the relative importance of variables, or specific combinations of variables, that predict the occurrence of untoward ischemic events could greatly enhance the management of patients with CAD.

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Comparison of SPECT Using Technetium-99m Agents and Thallium-201 and PET for the Assessment of Myocardial Perfusion and Viability

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This report reviews the applications of tomographic imaging with current and new tracers in assessing myocardial perfusion and viability. Multiple studies with thallium-201 (TI-201) single photon emission computed tomography (SPECT) imaging for the detection of coronary artery disease (CAD) have demonstrated high sensitivity, high rates of normalcy and high reproducibility. In assessing viability, fixed defects are frequently detected in viable zones in 4-hour studies with TI-201 imaging. Redistribution imaging performed 18 to 72 hours after injection or reinjection of TI-201 before 4-hour redistribution imaging has been shown to improve accuracy of viability assessment. TI-201 SPECT studies are limited by the suboptimal physical properties of TI-201, which result in variable image quality. The 2 new technetium-99m (Tc-99m) - labeled myocardial perfusion tracers offer the ability to inject much higher amounts of radioactivity, making it possible to assess ventricular function as well as myocardial perfusion from the same injection of radiotracer. Tc-99m sestamibi has very slow myocardial clearance, which allows for prolonged imaging time and results in image quality superior to that obtained with TI-201 and Tc-99m teboroxime. The combination of minimal redistribution of Tc-99m sestamibi and high count rates makes gated SPECT imaging feasible, and also permits assessment of patients with acute ischemic syndromes by uncoupling the time of injection from the time of imaging. The combination of high image quality and firstpass exercise capabilities may lead to a choice of this agent over TI-201 for assessment of chronic CAD. Tc-99m teboroxime is efficiently extracted by the myocardium in proportion to myocardial perfusion even at extremely high flow rates; however, this tracer demonstrates rapid myocardial washout, necessitating the completion of images very quickly after injection and generally resulting in suboptimal

image quality. Positron emission tomography (PET) has been applied with both rest and stress myocardial perfusion studies using rubidium-82, which has recently become commercially available, or nitrogen-13 ammonia. Although PET is clearly established as highly accurate for noninvasive detection of CAD, there are still divergent views as to whether PET is more accurate than TI-201 SPECT for these studies. No direct comparisons have been made with attenuation-corrected TI-201 SPECT or with the newer Tc-99m myocardial perfusion imaging agents. With respect to myocardial viability, studies using PET with fluorine-18 fluorodeoxyglucose remain the "gold standard." The principal limitations of this approach are the high costs of equipment and radiopharmaceuticals. The availability of multiple excellent agents for the scintigraphic assessment of myocardial perfusion is likely to greatly expand the use of nuclear cardiology techniques and to result in the ability to choose a particular agent to fit a given clinical situation.

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wide variety of radiopharmaceuticals will soon be available for the assessment of myocardial perfusion and viability. We present a clinical overview of the usefulness and limitations of the individual tracer approaches. Since single photon emission computed tomography (SPECT) has been shown to be more accurate than planar imaging for assessment of disease localization and extent, 1-3 comments with respect to thallium-201 (T1-201) and the technetium-99m (Tc-99m) agents will be limited to assessment by SPECT. It must be noted from the outset, however, that SPECT is far more technically demanding than planar imaging and has many more sources for artifacts that can result in false-positive studies. The discussion in the current review assumes careful attention to issues of SPECT quality control.

THALLIUM-201 TOMOGRAPHY

Tl-201 SPECT has matured as a noninvasive method for assessment of both myocardial perfusion and viability (Table I). With respect to myocardial perfusion, its application has been validated both with exercise and dipyridamole studies as accurate for detecting, localizing and evaluating the extent and severity of coronary artery disease (CAD). Techniques for quantitatively analyzing Tl-

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TABLE I Thallium-201 Single Photon Emission Computed Tomography

Perfusion

High sensitivity for coronary artery disease

High normalcy rate

High reproducibility

Viability

4-hour fixed defects frequently viable

Late imaging (18-72 hours) or reinjection improves

viability assessment

Limitations

Suboptimal physical properties result in variable image quality

201 SPECT have been developed and validated and are widely available. These techniques have demonstrated both excellent transportability between centers4 and high reproducibility.5 With respect to detection of CAD defined by angiographic stenoses of ≥50% luminal narrowing, published reports with quantitative analysis indicate a sensitivity of approximately 94%, a normalcy rate (frequency of the test being normal in patients with a low likelihood of CAD) of 82% and a specificity of between 50 and 90%^{4,6-9} (Table II). In this context, the term normalcy rate is used to distinguish patients deemed to be normal by pre-Tl-201 likelihood of disease from those called normal on the basis of coronary angiography. The low specificity of Tl-201 SPECT in some reports is likely the result of a posttest referral bias described by our group in which positive test responders are preferentially referred for catheterization. 10 This effect markedly reduces specificity and slightly increases sensitivity. 4 With current techniques it is estimated that the true sensitivity and specificity of Tl-201 SPECT are likely to be approximately 90 and 82%, respectively.

With time, the normalcy rate of Tl-201 SPECT may become higher than the currently reported 82%. Increasing knowledge of sources of technical artifacts such as patient motion¹¹ and "upward creep"¹² will decrease the frequency of false-positive studies. In addition, prone imaging has recently been demonstrated to markedly reduce attenuation artifacts in the inferior wall and basal septum that were frequent sources of false-positive studies. ^{13–15} In the absence of a special imaging table with a cardiac "cutout," however, this position has been reported to result in artifactual defects in the anterior wall. ¹⁶

The principal limitation of Tl-201 scintigraphy for assessment of myocardial perfusion relates to the suboptimal physical properties of the radionuclide with its lowerthan-ideal photon energy (68 to 83 keV) and long halflife (73 hours). The low energy results in increased attenuation and scatter compared to that seen with technetium-99m agents. The long half-life also places a limitation on the injected dose relative to the dose of technetium-99m that could be used. These factors necessitate prolonged imaging intervals and result in less than ideal image count density. Image quality with Tl-201 SPECT is dependent on a variety of technical factors, a principal one of which is count density. Although many centers are clearly producing routine SPECT TI-201 studies of good to excellent image quality, this quality appears to be highly variable, particularly in centers per-

	RCA Total	Spec Sens Spec Sens Spec	• 75% •	(178/196) (103/137) (145/147) (242/313)	91% 94% 91%	(66/72) (46/49) (50/55) (131/144)	%88 %88 %86	• (126/132) (93/104) • (92/106) (219/278) (313/352)	68% 84% 62% 77%	(98/145) (118/141) (63/101) (299/386)	60% 82% 71% . 80%	(29/48) (56/68) (30/42) (165/207)	84% 83% 84% 80%	(497/593) (416/499) (380/451) (1,056/1,328)	photon emission computed tomography; T1-201 = thallium-201.
	ГСХ	Sens Spec						(51/78) • (126/132)							y; Spec = specificity; SPECT = single photon emission computed tomography
11 by SPECT Imaging	LAD	Sens Spec				(57/63) (38/41)		(75/96) (95/114)					80% 83%		ns = sensitivit
ecificity of Quantitative T1-20	Norman	Spec Rate	87% —	(65/75) —	91%	(20/22) —	74%	(23/31) —	44% 82%	(20/46) (62/76)		(10/18) (24/28)	72% 83%	(138/192) (86/104)	LAD = left anterior descending; $LCX = left$ circumflex; $RCA = right$ coronary artery; Se
TABLE II Sensitivity and Specificity of Quantitative T1-201 by S	Overall	Sens	Mahmarian 87%		Tamaki 98%	et al ⁶ (80/82)	DePasquale 95%	et al ⁸ (170/179)		et al ⁴ (184/196)	Maddahi 95%	et al ⁷ (87/92)	Total 93%	(713/770)	LAD = left anterior descending; LCX =

TABLE III Technetium-99m Sestamibi

Perfusion

High sensitivity for CAD

High normalcy rate

Possibly more accurate for CAD than T1-201

High resolution images

Gated SPECT feasible

Useful in acute ischemic syndromes (uncoupling of injection

Function

First-pass rest or exercise ventricular function with perfusion study Viability

High correlation with 201 redistribution

Limitations

Differentiation of resting schemia from infarction

CAD = coronary artery disease; other abbreviations as in Table II.

forming a relatively low volume of studies. In addition, the physical properties of Tl-201 make it particularly limited with respect to image quality in obese patients or patients with large breasts. Furthermore, application of Tl-201 SPECT in acute ischemic syndromes is limited, since Tl-201 redistributes into areas of ischemia, thus necessitating imaging very soon after injection if the aim is to assess the extent, severity and location of hypoperfusion in the myocardium.

With respect to assessment of myocardial viability, reversible defects are highly predictive of viable myocardium.17 Defects that are conreversible at 4-hour imaging, however, frequently are viable as assessed by postoperative improvement in Tl-201 uptake or positron emission tomographic (PET) patterns. 17-21 Late redistribution imaging (18 to 72 hours after injection) substantially improves the ability of Tl-201 to predict myocardial viability. 17,18 These late reversible defects have been reported to be frequent, occurring in approximately 50% of patients and 20% of segments with fixed defects at 4 hours.22 However, a significant proportion of defects that are nonreversible at 24 hours (37% in our recent study¹⁷) still demonstrate improvement after successful revascularization. Preliminary data have suggested that a modification of the standard Tl-201 injection protocol may further

improve the ability of this tracer to predict myocardial viability. Dilsizian and associates 23,24 have demonstrated that a resting reinjection protocol improves the assessment of myocardial viability when 4-hour nonreversible defects are noted. In this setting, improvement of Tl-201 defects after reinjection of 1 mCi of Tl-201 has been shown to be predictive of improvement in asynergy after revascularization²³ and of myocardial viability using fluorodeoxyglucose and PET.24

TECHNETIUM-99m IMAGING AGENTS

The Tc-99m agents Tc-99m sestamibi and Tc-99m teboroxime are likely to be approved for clinical use by the Food and Drug Administration in 1990 for assessment of myocardial perfusion. Both agents have a clear advantage over Tl-201 because Tc-99m has physical characteristics ideal for gamma camera imaging. The favorable radiation dosimetry with Tc-99m-based radiopharmaceuticals allows injection of much larger amounts of radioactivity than is possible with Tl-201, making it possible to perform first-pass exercise studies of ventricular function followed by myocardial perfusion imaging using a single tracer injection. The 2 Tc-99m agents, however, have clearly different physiologic characteristics, resulting in differing properties with respect to assessment of myocardial perfusion and viability.

TECHNETIUM-99m SESTAMIBI

Tc-99m sestamibi has physiologic characteristics that allow for high resolution myocardial perfusion imaging (Table III). Although the extraction fraction of Tc-99m sestamibi is lower than that of Tl-201, the uptake of the former is parallel to that observed with Tl-201 in the flow ranges associated with rest and exercise. 25,26 The myocardial residence time is longer with Tc-99m sestamibi, which has a myocardial clearance half-time of approximately 5 hours. 25,27 There is also a more prompt hepatobiliary excretion (half-time approximately 30 minutes)28 than with Tc-99m teboroxime, so that there is little interference of hepatic uptake with visualization of the inferior left ventricular wall with Tc-99m sestamibi. The long

TO THE SECOND					Specificity	(%)					
	Sensitivity (%)					erall					
	Overall		Individual \	/essel	Normal Ar	teriogram	Low Likelihood Individua		Individual \	Vessel	
	Tc-MIBI	T1-201	Tc-MIBI	T1-201	Tc-MIBI	T1-201	Tc-MIBI	T1-201	Tc-MIBI	T1-201	
Kiat et al ³⁴ Kahn et al ³⁵	14/15 (93) 36/38	12/15 (80) 32/38	31/35 (87) 59/75 (79)	27/35 (77) 45/75 (60)	3/4 (75)	3/4 (75)	17/17 (100)	13/17 (77)	19/22 (86) 28/39 (72)	19/22 (86) 27/39 (69)	
Iskandrian et al ³⁶ Total	(95) 23/28 (82) 73/81 (90)	(84) 23/28 (82) 67/81 (83)	90/110	72/110 (66)	11/11 (100) 14/15 (93)	9/11 (82) 12/15 (80)	17/17 (100)	13/17 (77)	47/61 (77)	46/61 (75)	

* ≥50% stenosis considered significant CAD.

Low likelihood = patients with <5% likelihood of CAD; normal arteriogram = patients with normal coronary arteriogram; Tc-MIBI = technetium-99m sestamibi; other abbreviations as in Tables II and III.

half-time for myocardial clearance allows imaging for longer periods than is possible with Tc-99m teboroxime, resulting in SPECT images of very high count density. These images are thereby of higher resolution than is observed with Tl-201 or Tc-99m teboroxime SPECT. In addition, the prolonged myocardial steady state in count distribution and the higher count rate allow for the performance of gated SPECT,29 which is not feasible with Tc-99m teboroxime or Tl-201. Minimal redistribution of Tc-99m sestamibi allows for an uncoupling of the time of injection from the time of imaging. This unique feature makes Tc-99m sestamibi the only myocardial perfusion tracer well suited to tomographic imaging of patients with acute ischemic syndromes, a feature already proven important in assessing the effects of thrombolytic therapy^{30,31} and in evaluating patients with unstable angina.³² This is also the only tracer well suited to assessing interventions in the cardiac catheterization laboratory with SPECT, again due to the ability to separate the time of injection from the time of imaging. This application is discussed by Braat et al elsewhere in this supplement.33

To date the published reports on SPECT Tc-99m sestamibi myocardial imaging have demonstrated very high sensitivity, specificity and normalcy rates for overall detection of CAD, reported as 90, 93, and 100%, respectively.34-36 Sensitivity and specificity for individual vessel detection of 82 and 77%, respectively, have also been observed (Table IV). All of these values are numerically higher than those observed in the same patient populations with Tl-201 (Table IV); however, the relatively small number of patients studied with Tc-99m to date does not allow a definitive statement with respect to the significance of this trend toward improvement in diagnostic accuracy. In addition, clear superiority in image quality has been reported with Tc-99m sestamibi studies compared to Tl-201,35 which may explain the apparent improvement in accuracy for CAD detection. The improved physical characteristics with respect to attenuation might also be part of the explanation for the apparent improvement in specificity and normalcy rates. The preliminary data suggest that Tc-99m sestamibi imaging is likely to be as sensitive and specific as PET for assessment of myocardial perfusion. The results of the Phase III multicenter trial, as presented by Maddahi et al in another study in this supplement³⁷ reporting larger patient numbers from a wide variety of centers, have suggested equal sensitivity, specificity and normalcy rates for Tc-99m sestamibi and Tl-201 SPECT myocardial perfusion studies for detection of CAD.

The aforementioned information with respect to detection of CAD has been obtained with protocols that were optimized for Tl-201 imaging (i.e., they used the same reconstruction filters and, for the most part, an all-purpose collimator). Recent data have suggested that optimization of acquisition parameters (most importantly the use of a high-resolution collimator) and filters results in substantial improvement in image quality. Preliminary experience in humans with optimized acquisition parameters has revealed superior image quality compared to that observed in the previous Tc-99m sesta-

TABLE V Comparison of Type of Defect by Tc-99m Sestamibi and T1-201 Myocardial Perfusion SPECT: Segmental Analysis

	Tc-99m Sestamibi (%)				
《拉西斯》	Normal	Reversible	Nonreversible		
T1-201			THE WALLS		
Normal	1,127 (74)	25 (2)	5 (4)		
Reversible	41 (3)	87 (6)	11 (1)		
Nonreversible	28 (2)	14(1)	182 (12)		
Exact segmental agreement					
Kiat et al ³⁴	653/720	(91)			
Iskandrian et al ³⁶	743/800				
Total	1,396/1,52				
Tc-99m = technetium-99m; other	er abbreviations	as in Table II.			

mibi studies. The specifics of this process of optimization and examples of its results are presented in this supplement in the report by Garcia et al.³⁹ Since inconsistency of image quality is one of the principal drawbacks of myocardial perfusion imaging with Tl-201, it is suspected that improved image quality will be one of the principal reasons for the preferential use of Tc-99m sestamibi over Tl-201. This improvement in image quality may lead to decreased variability in myocardial perfusion imaging from center to center and to improved interpreter confidence. These optimized protocols could also lead to further improvements in sensitivity or specificity, or both, for detection of CAD.

With respect to the assessment of myocardial viability, published reports to date have demonstrated excellent agreement between the type of SPECT defect observed by Tl-201 scintigraphy and by Tc-99m sestamibi. 34,36 Using a 2-day protocol, exact segmental agreement for normal, reversible and nonreversible segments has been observed in 92% of 1,520 segments (Table V). Importantly, evidence of nonreversible defects by Tc-99m sestamibi has been seen in only 1% of patients with reversible defects by Tl-201. These comparisons, however, have been made only with standard stress-redistribution Tl-201 imaging protocols. It remains to be seen whether late redistribution Tl-201 protocols^{17,18} or reinjection Tl-201 protocols (which take advantage of both Tl-201 redistribution and the reinjection process)^{23,24} are superior to rest-stress Tc-99m sestamibi images for assessment of viability. Although not yet explored, fundamental principles would suggest that rest-redistribution Tl-201 scintigraphy might be more effective than rest Tc-99m sestamibi imaging for differentiating segments with resting ischemia from infarcted segments. An intriguing possibility has been raised of using nitroglycerin before administration of Tc-99m sestamibi when viability is being assessed in patients with suspected resting ischemia (Galli, personal communication).

One of the principal advantages of both of the technetium-99m agents is the ability to perform studies of exercise ventricular function and myocardial perfusion from the same injection of radioactivity. Borges-Neto et al⁴⁰ have demonstrated the feasibility of this combined perfusion and function approach using treadmill exercise first-pass studies in conjunction with a multicrystal scintilla-

TABLE VI Technetium-99m Teboroxime

Very high myocardial extraction Rapid myocardial washout High throughput feasible

Function

First-pass rest or exercise ventricular function with perfusion study Viability

Not adequately studied

Limitations

Rapidly changing distribution limits imaging time (suboptimal for high-resolution imaging)

May require multidetector camera and vasodilator (as opposed to exercise) for SPECT

SPECT = single photon emission computed tomography.

tion camera. Although there was general correlation between ejection fraction at rest and during exercise and the respective size of SPECT perfusion defects, wide variability in perfusion defect size was seen in patients with mild reduction in exercise ventricular function, which suggests a degree of independence between these markers. 40 The details of this combined first-pass and SPECT approach are described in the report in this supplement by Jones et al.41 We have obtained similar preliminary results using essentially the same treadmill exercise first-pass and similar SPECT myocardial perfusion Tc-99m sestamibi protocols. 42 This approach offers promise for providing efficient and cost-effective information that previously would have required the performance of separate ventricular function and myocardial perfusion studies.

TECHNETIUM-99m TEBOROXIME

This new agent has very high myocardial extraction throughout a broad range of flow rates (Table VI).43-45 Extraction is higher than observed with techniques using Tl-201, Tc-99m sestamibi and PET using rubidium-82 and nitrogen-13 ammonia. Conceptually, this quality could make Tc-99m teboroxime the most sensitive tracer for the early detection of CAD when coupled with a highly potent, hyperemic stress. However, the radiopharmaceutical also demonstrates rapid washout from the myocardium with a clearance half-time from the heart of 10 to 15 minutes. Imaging with Tc-99m teboroxime must thus be completed very rapidly. Prominent liver uptake with slow clearance (half-time approximately 1.5 hours) can impair visualization of the inferior left ventricular wall. Early studies have suggested that differential washout may occur between normal and abnormal zones.46 The advantage of this differential washout is that a very early image (possibly between 1 and 4 minutes after injection) might be obtained representing the stress myocardial perfusion distribution, and a delayed image might be obtained soon thereafter (approximately 10 to 15 minutes after injection), with viable but ischemic areas demonstrating slower washout of the tracer. This property, theoretically, could result in the equivalent of stress-redistribution TI-201 imaging being performed in approximately 15 minutes. Alternatively, the rapid myocardial washout allows for resting reinjection soon after the com-

pletion of the stress images. Although the rapid imaging necessitated by the kinetics of this tracer may be feasible with planar imaging, such rapid imaging after exercise may be difficult using conventional SPECT cameras, which even with high count rates would require several minutes for data acquisition. In clinical practice, imaging in the early postexercise state is typically delayed for several minutes due to the necessity for patient monitoring and to avoid false-positive defects due to "upward creep of the heart" observed on very early postexercise images. 12 If this delay were applied to Tc-99m teboroxime SPECT, data acquisition would begin in the phase in which slower washout of Tc-99m teboroxime from ischemic zones may already have obscured stress perfusion defects. Tc-99m teboroxime SPECT imaging in the very early postinjection state could, however, have interesting potential through the combined use of a multidetector camera, reducing the SPECT acquisition time, and a potent coronary vasodilator such as intravenous adenosine⁴⁷ or dipyridamole⁴⁸⁻⁵⁰ that could be given while the patient was in position for imaging within the orbit of the SPECT device. An additional limitation of the very rapid washout rate from the myocardium is that the absence of a prolonged steady state of radioactivity within the myocardium reduces the total imaging time available, thereby resulting in less-than-optimal image quality. Gated SPECT would essentially not be feasible with standard SPECT instrumentation using this agent. The tracer also could not be used conveniently for SPECT in patients with acute ischemic syndromes since the SPECT cameras are rarely near these patients. Using rapid image acquisition protocols, however, early data using planar acquisition have indicated high sensitivity and specificity for CAD with this new agent. 51 More details of the efficacy of Tc-99m teboroxime studies, including information suggesting that SPECT studies can be performed with this agent, are provided in the review by Johnson and Seldin⁵² in this supplement.

With respect to myocardial viability, the differential washout rate observed in normal and ischemic myocardium raises interesting possibilities for rapid assessment. Whether this differential clearance could be used with resting injections to distinguish resting hypoperfused but viable zones from zones with myocardial infarction has not yet been studied.

TABLE VII Comparison of the Physiologic Properties of Tc-99m Sestamibi and Tc-99m Teboroxime

		The state of the s
Agent	Tc-99m Sestamibi	Tc-99m Teboroxime
Class Extraction fraction (peak)	Isonitrile 0.65	BATO compound 0.90
Clearance T _{1/2} Heart Liver	5 hours 30 minutes	10–15 minutes 90 minutes
Redistribution (differential washout) Dose	Minimal 30 mCi	Yes 30 mCi

BATO = boronic acid adduct of technetium dioxime; Tc-99m = technetium-99m; $T_{1/2}$ = half-life time.

The comparative physiologic properties and imaging properties of Tc-99m sestamibi and Tc-99m teboroxime are listed in Tables VII and VIII. An excellent review of the pharmacokinetics of Tc-99m sestamibi, Tc-99m teboroxime and Tl-201 is provided in this supplement by Meerdink and Leppo.⁵³

POSITRON EMISSION TOMOGRAPHY

Recent advances in scanners for PET have resulted in the clinical availability of systems with high resolution (approximately 5 mm) and the ability to image the entire heart in 1 view (Table IX). The generator-produced positron pharmaceutical rubidium-82 (half-life, 75 seconds) has recently been approved by the Food and Drug Administration and allows the performance of PET of perfusion without requiring a cyclotron. For centers desiring the flexibility of imaging multiple types of radiopharmaceuticals, medical cyclotrons that can be housed within nuclear medicine departments have been developed. The tracer most widely used for the assessment of myocardial viability, fluorine-18 fluorodeoxyglucose, has a 110-minute half-life. This agent can be provided by either an inhouse cyclotron or by a cyclotron in the general geographic region of a given facility. Facilities with cyclotrons most commonly use nitrogen-13 ammonia (half-life, 10 minutes) for perfusion imaging.

With respect to assessment of myocardial perfusion, PET has been demonstrated to be highly accurate for the detection of CAD. 54-57 Based on available data, however, the superiority of PET compared to Tl-201 SPECT has not yet been established. Demer and associates⁵⁴ assessed dipyridamole PET using coronary flow reserve derived from quantitative coronary angiography to determine the presence of significant CAD in 193 patients, 69 of whom had prior myocardial infarction. If a coronary flow reserve ≥4 was considered normal, dipyridamole PET had a sensitivity of 94% and a specificity of 74% for detecting CAD. If a coronary flow reserve ≥3 was considered normal, dipyridamole PET had a sensitivity of 82% and a specificity of 95%. These values are strikingly similar to those observed with SPECT and planar Tl-201 imaging, respectively (Fig. 1). Few studies have directly compared stress PET and Tl-201 studies in the same patients. Tamaki et al,55 comparing exercise nitrogen-13 ammonia PET and Tl-201 SPECT images in the same patients. demonstrated no significant difference in sensitivity and specificity for detection of CAD or identification of dis-

TABLE VIII Comparison of the Imaging Properties of Tc-99m Sestamibi and Tc-99m Teboroxime							
Agent	Tc-99m Sestamibi	Tc-99m Teboroxime					
Begin imaging	30–60 minutes	1 minute					
Complete rest-stress	3–4 hours	90 minutes					
Total myocardial counts	High	Transiently high					
SPECT	Yes	Possible (quickly)					
Gated SPECT	Yes	No					
First pass	Yes	Yes					

TABLE IX Positron Emission Tomography

Perfusion (Rb-82 or N-13 NH₃) Similar sensitivity to T1-201 Question if slightly higher specificity Viability (F-18 FDG)

Highly predictive of improvement after revascularization Probably most accurate test

Limitations

High costs of equipment and radiopharmaceuticals

 $F-18\,FDG = fluorine-18\,fluorodeoxyglucose;\,N-13\,NH_3 = nitrogen-13\,ammonia;\,Rb-82 = rubidium-82;\,T1-201 = thallium-201.$

ease in individual vessels. Stewart et al⁵⁶ have suggested similar sensitivity but slightly higher specificity of rubidium-82 PET compared to Tl-201 SPECT in a group of patients having exercise or dipyridamole stress studies with both approaches. The Tl-201 SPECT examination in this study appears to have been subject to more posttest referral bias than the study of PET (i.e., patients had the Tl-201 study ordered for clinical purposes). The positive test responders were then more likely than the negative responders to be catheterized. The PET study then frequently followed catheterization (Schwaiger, personal communication). Go et al,⁵⁷ in a study using 1 dipyridamole stress test for sequential rubidium-82 PET and Tl-201 SPECT studies in the same patients, have reported no significant difference in specificity but slightly higher sensitivity with PET. The improved specificity of Tl-201 in this study may be related to the use of a 360° SPECT acquisition. This acquisition also has the effect of reducing sensitivity, as might their use of injection of Tl-201 after the performance of the PET examination when the

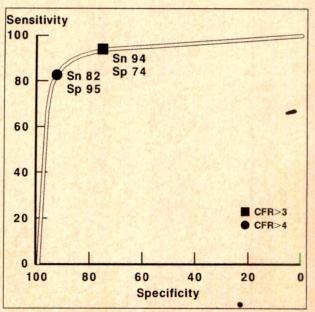


FIGURE 1. Receiver operating characteristic curve of results of dipyridamole perfusion positron emission tomography in 193 patients. The results for sensitivity (Sn) and specificity (Sp) of the 2 criteria are very similar to published results using planar and single photon emission computed tomography thallium-201 exercise scintigraphy. CFR = coronary flow reserve predicted from quantitative coronary angiography. 54

dipyridamole effect might not be maximal. There are no data comparing the perfusion of PET to that of SPECT using the new Tc-99m myocardial perfusion imaging agents.

With respect to myocardial viability, Tillisch et al58 have demonstrated that fluorine-18 fluorodeoxyglucose PET is highly predictive of postrevascularization improvement in regional myocardial asynergy. These results were somewhat more favorable than those of Tamaki et al, 59 who more recently demonstrated that 78% of asynergic regions with evidence of viability by PET demonstrated improved function postoperatively, compared to 22% of regions without evidence of viability by PET. Brunken et al have demonstrated that fluorine-18 fluorodeoxyglucose PET frequently demonstrates evidence of myocardial viability in regments with nonreversible Tl-201 SPECT defects at 4 hours⁶⁰ and at 24 hours.⁶¹ In addition, Fudo et al,62 in a study evaluating the relation of perfusion and viability by PET in the territory of prior myocardial infarction, showed that nitrogen-13 ammonia and fluorodeoxyglucose "mismatch" is frequent in the apparently infarcted territory, suggesting an element of residual viability. The investigators also showed that evidence of moderately extensive viable myocardium with fluorine-18 fluorodeoxyglucose uptake may be present even in functionally dyskinetic myocardial regions. The clinical significance of this finding, which at times may represent small regions of viable myocardium in largely infarcted zones, remains to be determined.

PET probably represents the most accurate test for assessment of regional myocardial viability in medicine today. As previously noted, however, a preliminary comparison to a new Tl-201 reinjection SPECT protocol has suggested that Tl-201 SPECT and fluorine-18 fluorodeoxyglucose PET may have fewer discrepancies than reported with Tl-201 redistribution SPECT.²⁴ Thus, the proportion of patients who might benefit from analysis of myocardial viability using fluorine-18 fluorodeoxyglucose PET after Tl-201 reinjection studies remains in question.

The principal limitations of PET are related to cost. The various components required for PET are all very expensive, with the positron emission tomographic scanner costing approximately \$2,000,000, the cyclotron approximately \$1,500,000 and the rubidium-82 generator having a monthly cost of approximately \$20,000.63

CONCLUSION

New developments with Tc-99m agents and refinements in Tl-201 imaging and PET portend a bright future for myocardial perfusion scintigraphy. With the wide variety of tracers available, the clinician will soon be able to choose the most appropriate agent for a particular clinical settieg. This choice will be determined by a combination of clinical considerations, cost factors and the equipment available in a given laboratory.

Acknowledgment: The authors gratefully acknowledge the excellent editorial help of Trudy Gibbs and Dorothy Scott and the secretarial assistance of Judy Manders.

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Technetium-99m Sestamibi Myocardial Imaging: Same-Day Rest-Stress Studies and Dipyridamole

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Unlike thallium-201, technetium-99m (Tc-99m) sestamibi does not redistribute in the myocardium after injection. Thus, 2 separate injections, 1 at rest and the other at stress (or after dipyridamole), are required to diffe entiate ischemia from scar. From a physical viewpoint, a 24-hour interval between the 2 injections is preferable for detection of coronary artery disease (CAD) with Tc-99m sestamibi imaging. However, same-day studies are more convenient in clinical practice. Results of studies using different Tc-99m sestamibi injection protocols are presented with emphasis on the advantages of a rest-stress injection sequence with a low dose at rest (7 mCi) followed 2 hours later by a higher dose at stress (25 mCi). A prospective study was conducted in a patient population with proven CAD using same-day studies to compare a reststress (7 and 25 mCi, respectively) to a stress-rest (7 and 25 mCi) Tc-99m sestamibi injection sequence. There was an agreement in 87.3% of the analyzed segments between the 2 protocols. However, the largest discordance for type of defect applied to 7.4% of the segments judged ischemic in the rest-stress protocol, which were called scars on stress-rest. This study showed that a rest-stress sequence is preferable when using a same-day protocol with a short time interval (<2 hours) between the 2 Tc-99m sestamibi injections because the rest image performed initially represents a "true" rest study, which is not necessarily the case with the stress-rest sequence.

Preliminary studies were performed to evaluate dipyridamole with Tc-99m sestamibi imaging in normal subjects and in patients with CAD. These studies showed that treadmill and dipyridamole Tc-99m sestamibi imaging are comparable and the results are similar to those obtained with thallium-201.

(Am J Cardiol 1990;66:80E-84E)

'nlike thallium-201, technetium-99m (Tc-99m) sestamibi does not redistribute in the myocardium after injection. This offers 2 interesting advantages: excellent flexibility for imaging time after the stress injection and a lack of problems with underestimation of ischemia severity due to early redistribution (as sometimes seen with thallium-201).

SAME-DAY STUDIES

Because of the absence of significant redistribution, separate injections of this new myocardial perfusion agent are required to differentiate ischemia from scar and this may present a problem in clinical practice. Several different protocols for the 2 injections may be used Given the 6-hour half-life of Tc-99m, a 24-hour separation between the 2 injections is ideal to minimize background radioactivity. Ideally, this would be performed with the stress study first, because if it is normal, the rest study may not be needed. Although preferred from the technical standpoint, this protocol using a 24-hour interval between the 2 injections is far from being ideal ir clinical practice where having all of the information on a single day would be highly preferred. Tc-99m sestamib can be injected at stress followed 24 or 48 hours later by a second injection at rest.

Thus, for practical reasons, the optimal time interval used for performing Tc-99m sestamibi studies should be approximately 4 hours, which is similar to that used for thallium-201 imaging. Using this alternative, 1 dose of Tc-99m sestamibi is injected at stress (or at rest) followed the same day by a second similar or higher dose at rest (or at stress). The 3 major variables to consider in a same-day Tc-99m sestamibi injection protocol are: (1) the time interval between rest and stress injections; (2) the injected amount of activity for each injection; and (3) the sequence of injections (rest-stress or stress-rest).

A previous study compared the same-day injection protocol with a 24-hour interval between rest and stress studies in 15 patients with evidence of significant coronary artery disease (CAD) during both thallium-201 and coronary angiography. On the same-day protocol, planar imaging (10 minutes/view, 3 views) was performed 1 hour after a rest injection of Tc-99m sestamibi (7 to 10 mCi). After completing the rest study, patients received 25 to 30 mCi of Tc-99m sestamibi at stress and images were again obtained 60 minutes later. Two days later (long time-interval protocol) a stress study alone was repeated using 10 mCi of Tc-99m sestamibi with the same imaging parameters. Qualitative and quantitative comparisons between the same-day and the long timeinterval studies were performed by 4 experienced observers. Both protocols showed the same number of ischemic

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segments (52 of 225) and fixed defects (19 of 225). Normal/ischemic wall ratios were 1.33 ± 0.12 for the sameday and 1.28 ± 0.10 for the long protocol (difference not significant). Thus, this study using a rest-stress injection sequence showed that same-day studies with Tc-99m sestamibi can be useful and give results similar to the 2-day protocol for detection and characterization of perfusion defects.

The Tc-99m sestamibi doses of 7 to 10 mCi at rest and 25 to 30 mCi at stress were empirically chosen from previous preliminary data obtained in our laboratory. Originally, we have used a dose of 5 mCi at rest, but this dose resulted in relatively poor counting statistics. Therefore, the dose was increased to 7 to 10 mCi. The stress/ rest dose ratio of 3 to 3.5 was also empirically determined. taking into consideration the time interval of 2 hours and the rest-stress sequence. A lower ratio can be used, but the time interval between both injections would have to be increased. A time interval of 5 to 6 hours between the 2 Tc-99m sestamibi injections is not much more convenient than a 24-hour interval in clinical practice because allowance must be made for an additional 1.5 to 2 hours after the last injection to complete the imaging. Thus, only a few patients/day can be studied with 1 gamma camera using a 5- to 6-hour interval between both injections.

The next step was to compare the rest-stress and stress-rest injection sequence for same-day Tc-99m sestamibi studies.2 Eighteen patients with either an abnormal thallium-201 scan or abnormal coronary angiography were prospectively studied with 2 Tc-99m sestamibi injection protocols. The rest-stress study (Fig. 1) was performed as follows: Tc-99m sestamibi (7 mCi) was injected at rest and single photon emission computed tomography (SPECT) imaging was performed 60 minutes later. Immediately after the rest study, patients were injected at peak stress with Tc-99m sestamibi (25 mCi) and a SPECT study was repeated 1 hour later. Within 3 days after completion of this study, patients were submitted to the stress-rest protocol. In this protocol, SPECT imaging was done 1 hour after administering Tc-99m sestamibi (7 mCi) at stress. This was followed by an injection of Tc-99m sestamibi (25 mCi) at rest with a SPECT study performed 60 minutes later. SPECT acquisition was performed on a Picker Dyna digital rotating camera and SX-300 gantry linked to a PCS-512 computer. The system consists of a large field-of-view gamma camera with a 0.37-inch thick sodium iodide crystal, 60 photomultiplier tubes and a low-energy, ultrahigh-resolution, parallelhole collimator. A symmetrical 15% window was centered at 140 keV, and images were acquired into a 64 X 64 computer matrix. Sixty-four 30-second projections (for the initial study with 7 to 8 mCi) and 20-second projections (for the second study with 25 mCi) were acquired over a 180° arc, extending from the 45° left posterior oblique to the 45° right anterior oblique view. Corrections for center of rotation offset, field nonuniformity (40 million count Tc-99m uniformity flood) and attenuation ($\mu = 0.12$) were performed before reconstruction. Myocardial sections were reconstructed in horizontal long, vertical long and short axes. Circumferential

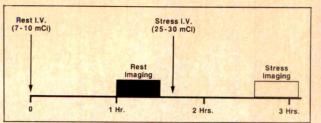
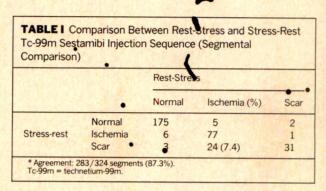


FIGURE 1. Schematic representation of technetium-99m sestamibi studies performed on the same day with a short time interval (<2 hours) between the rest and stress injections.

I.V. = intravenous.



count profiles extending from the apex to the base (2dimensional polar map) were generated for all studies. The left ventricle in each midplane was arbitrarily divided into 6 segments, which were scored to represent normal, ischemic or scar tissue on the basis of a transient or fixed defect. A total of 324 segments was interpreted blindly by 3 observers (Table I) with respect to the scans being normal, showing ischemia or a scar. There was agreement in 283 of 324 (87.3%) segments between the 2 protocols (Fig. 2). However, the largest discordance for type of defect applied to 24 segments (7.4%) judged ischemic in the rest-stress protocol that were called scars on stress-rest (Fig. 3). Stress images from both protocols were judged similar in 17 patients. In 1 patient, both injection sequences showed the same defects, but the ischemia was judged to be more significant with the stressrest protocol. The conclusion of this study was that a reststress sequence is preferable when using a same-day protocol with a short time interval (<2 hours) between the 2 Tc-99m sestamibi injections because the rest image performed initially represents a "true" rest study, which is not necessarily the case with the stress-rest sequence.

Advantages of rest-stress injection sequence: Better characterization of perfusion defect: The aforementioned study showed that 7% of the myocardial segments were normal on the rest images of the rest-stress protocol but showed persistent defects on the rest images of the stress-rest sequence. Thus, the injection of Tc-99m sestamibi (25 mCi) at rest was not able to completely fill in the significant defect created by the previous 7 mCi injection at stress

Uniform myocardial background for patients with ischemia: Since the rest study is performed first, there is

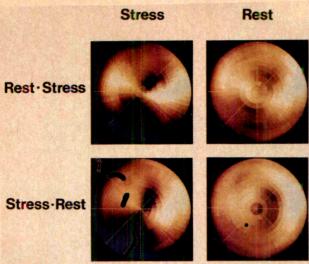


FIGURE 2. Technetium-99m sestamibi tomographic imaging (polar map representations) in a patient with 100% stenosis of the right coronary artery. Both rest-stress and stress-rest injection sequences show a similar ischemic defect involving the inferior wall of the left ventricle. (Reproduced with permission from Eur J Nucl Med.2)

no "contamination" from a previous Tc-99m sestamibi injection. In a patient with ischemia but without infarction, the ischemic defect will be seen on a relatively uniform myocardial background from Tc-99m sestamibi rest injections (Fig. 4). In the stress-rest protocol, myo-

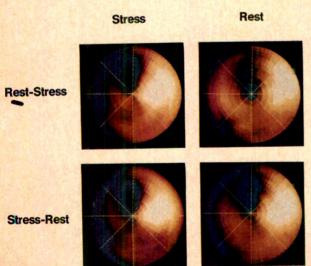


FIGURE 3. Technetium-99m sestamibi tomographic imaging in a patient with 100% stenosis of the left anterior descending coronary artery and 95% stenosis of the right coronary artery, who had a previous anterior wall infarction. The rest-stress sequence shows significant anteroseptal ischemia with a small fixed anteroapical defect, while the stress-rest sequence is more compatible with a nearly fixed anteroseptal defect. Significant anteroseptal ischemia with fixed anteroapical defects (as detected with the rest-stress sequence) were seen on the thallium-201 study. (Reproduced with permission from Eur J Nucl Med.2)

cardial background for the rest study will be nonhomogenous. The rest injection has to fill in the defect created by the stress injection, and this is difficult, particularly in patients with significant ischemia. Such patients will have a fixed or partially "reversible" defect (false diagnosis) on the stress-rest sequence. If the stress-rest sequence is used with a longer time interval or with a higher dose at rest, it is likely that results will improve.3,4

Larger difference of activity between both injections: Theoretically, the larger the difference in the amount of activity between the rest and stress injections, the greater will be the possibility to reduce background effects created by residual activity from the initial injection of Tc-99m sestamibi. For a given amount of injected activity, absolute myocardial uptake is higher at stress than at rest. Thus, the difference is greater with the rest-stress than with the stress-rest sequence, since the greatest amount of activity is injected at stress using the former protocol. Results of a phase I study of Tc-99m sestamibi showed that the myocardial uptake is 1.0% of injected dose at rest and 1.4% at stress.5 In our study, the reststress protocol used a dose of 7 mCi at rest (1.0% = 70 μ Ci) and 25 mCi at stress (1.4% = 350 μ Ci) for a ratio of 5-to-1 (350-to-70). The stress-rest sequence uses a 7 mCi dose at stress (1.4% = 98 μ Ci) and 25 mCi at rest $(1.0\% = 250 \,\mu\text{Ci})$ for a ratio of 2.5-to-1 (250-to-98). Thus, the difference in the amount of myocardial activity between the 2 Tc-99m sestamibi injections is doubled with the rest-stress sequence.

Lower dosimetry: The phase I study also showed that dosimetry is lower with a stress injection than with a rest injection of Tc-99m sestamibi. Thus, the rest-stress protocol (with 7 mCi at rest) provides better dosimetry than the stress-rest protocol (with 25 mCi at rest).

First-pass study: Tc-99m sestamibi is well suited for first-pass radionuclide angiography at stress because of the Tc-99m labeling. If allowed by the technical setup, the rest-stress protocol will be preferable using a stress dose of 25 mCi.6 If only 5- to 7-mCi doses were used for the stress study in a stress-rest sequence, exercise firstpass studies would not be feasible even with dedicated multicrystal cameras.

Conclusion: Same-day studies can be a useful alternative to the optimal 24-hour interval between 2 Tc-99m sestamibi injections for detection of CAD. When using same-day studies with a short time interval (<2 hours) between 2 Tc-99m sestamibi injections, the rest-stress sequence is preferable. The stress-rest sequence is a possible alternative but it would be necessary to use a longer time interval between the 2 injections or to increase the difference in the amount of injected activity.

DIPYRIDAMOLE STUDIES

Intravenous dipyridamole is recognized as a useful alternative to a treadmill stress test with thallium-201 myocardial imaging in patients unable to achieve an adequate level of exercise. If Tc-99m sestamibi imaging is accepted as a routine procedure in the detection of CAD, it is likely that dipyridamole will also play a significant role with this new radiopharmaceutical. Preliminary

studies have been performed to evaluate dipyridamole with Tc-99m sestamibi imaging in normal subjects and in patients with CAD.

Studies in normal subjects: A study was performed in our laboratory to determine and compare the blood clearance, myocardial uptake and heart-to-lung ratios of Tc-99m sestamibi after the treadmill stress test and dipyridamole. Ten normal volunteers were injected with Tc-99m sestamibi (10 mCi/70 kg) at peak stress and after dipyridamole infusion 7 days later. Blood samples were collected from 1 to 60 minutes after each Tc-99m sestamibi injection and planar images were obtained at 5 and 60 minutes. Regions of interest were placed over the heart, left lung and liver. Myocardial uptake (cpm/pixel/mCi) was also determined. Table II summarizes the results obtained in this normal subject population. Tc-99m sestamibi blood clearance is significantly faster after dipyridamole infusion (0.142 mg/kg/min for 4 minutes). This can be explained by dipyridamole-induced vasodilation and splanchnic pooling of the radiotracer, which causes a rapid splanchnic uptake and subsequent fast blood clearance. The heart/lung ratio was higher with dipyridamole than in the stress study. Since myocardial uptake is similar for the 2 types of cardiac stimulation, a decreased lung uptake should be responsible for the increased heart/lung ratio. These data differ from those obtained with thallium-201, where there is an increased thallium-201 myocardial uptake after dipyridamole and similar lung uptake after both stress and dipyridamole imaging. However, the resultant effect is the same, the heart/lung ratio being increased with dipyridamole. A similar study would have to be performed in patients with CAD to confirm these findings. The Tc-99m sestamibi heart/liver ratio is higher at stress than after dipyridamole. As with thallium-201, there is less splanchnic and liver uptake at stress. which explains the higher heart/liver ratio.

Studies in patients with coronary artery disease: A second study was undertaken to compare Tc-99m sestamibi to thallium-201 imaging after injection of dipyridamole.8 Twenty-seven patients referred for the evaluation of chest pain were prospectively studied with both thallium-201 and Tc-99m sestamibi dipyridamole planar imaging. A same-day injection protocol was used for Tc-99m sestamibi: Tc-99m sestamibi (7 to 8 mCi) was injected at rest and imaging was performed 60 minutes later. This was followed by an injection of Tc-99m sestamibi (25 mCi) after dipyridamole administration, with imaging obtained 60 minutes later. Analysis was performed by 3 blinded observers. The left ventricle was divided into 3 segments in each image. Comparison of thallium-201 with Tc-99m sestamibi studies showed agreement in 87.2% (212 of 243) of the myocardial segments (Table III). Both scans were normal in 9 patients. Abnormal thallium-201 and Tc-99m sestamibi studies were seen in 18 and 16 patients, respectively. This study showed that there is a good correlation in the results with thallium-201 and a same-day injection protocol of Tc-99m sestamibi using dipyridamole, both on a segmentby-segment basis and on a patient-by-patient comparison. These findings are similar to those reported in studies

(right coronary: 95%)

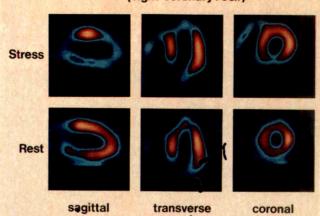


FIGURE 4. Technetium-99m sestant bi tomographic slices (3 different incidences) showing a significant ischemic defect of the inferior wall in a patient with a 95% stenosis of the right coronary artery. Both rest and stress technetium-99m sestamibi images were completed within 4 hours using a same-day injection protocol (initial rest injection with 8 mCi followed 2 hours later by a stress injection of 27 mCi).

TABLE II Comparison Between Treadmill and Dipyridamole Tc-99m Sestamibi

	Stress	Dip	p Value
Blood clearance (% 1 minute)	56 ± 4	24 ± 4	<0.001
Myocardial uptake (5 minutes)	109 ± 22	103 ± 21	NS
Myocardial uptake (60 minutes)	96 ± 20	90 ± 21	NS
Heart/lung (5 minutes)	2.7 ± 0.3	3.2±0.5	< 0.001
Heart/lung (60 minutes)	3.1 ± 0.5	3.8 ± 0.6	< 0.001
Heart / liver (60 minutes)	1.9 ± 0.5	1.3±0.3	< 0.001

TABLE III Comparison Between Tc-99m Sestamibi and Thallium-201 Dipyridamole Imaging: Segmental Analysis

		Tc-99m Sestamibi (%)				
		Normal	Ischemia	Scar		
	Normal	146 (60.0)	7	2		
Thallium-201	Ischemia	11	47 (19.2)	6		
	Scar	3	2	19 (8.0)		

comparing thallium-201 and Tc-99m sestamibi planar imaging with treadmill stress test.

In a third study, treadmill stress test was compared to dipyridamole Tc-99m sestamibi imaging in•17 patients referred for coronary angiography. Treadmill and dipyridamole studies detected 31 and 34 ischemic segments, respectively (difference not significant), while both studies showed 15 fixed defects.

In conclusion, these preliminary studies showed that treadmill and dipyridamole Tc-99m sestamibi imaging

A SYMPOSIUM: TECHNETIUM-99m IMAGING AGENTS

are comparable and have results similar to those obtained with thallium-201.

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Use of Technetium-99m Sestamibi to Determine the Size of the Myocardial Area Perfused by a Coronary Artery

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The value of the new radionuclide tracer, technetium-99m (Tc-99m) sestamibi, to demonstrate myocardial perfusion in areas supplied by specific coronary arteries was evaluated in patients injected with the agent during cardiac catheterization. Tc-99m sestamibi differs from thallium-201 in its physical characteristics (photon energy 140 keV), half-life (6 hours) and lack of significant redistribution, allowing its administration during an episode of chest pain or ischemia occurring outside the nuclear medicine laboratory with later imaging to visualize the distribution. In 13 patients Tc-99m sestamibi was administered intravenously during balloon-occlusion angioplasty. In 11 of 13 patients, defects of the single photon emission computed tomography images corresponded to the area made ischemic during angioplasty. In the remaining 2 patients, abundant collateral flow was present and no defects were seen. In a second study, 15 patients had Tc-99m sestamibi selectively injected into a coronary artery during angiography. Later imaging identified the area supplied by the artery injected. Tc-99m sestamibi imaging can detect perfusion defects associated with short episodes of ischemia, and the area supplied by the different coronary arteries.

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or over 15 years, thallium 201 (Tl-201) has been used for the evaluation of patients with suspected coronary artery disease. The physical characteristics of Tl-201 make it less than ideal for imaging purposes, and therefore several alternative agents have been evaluated. Technetium-99m (Tc-99m) sestamibi is an alternative myocardial perfusion imaging agent shown to have good biologic properties for clinical use: It has a half-life of 6 hours, is excreted quickly by the liver and kidneys, has a photon energy of 140 keV, has low lung uptake and has no side effects.

Tc-99m sestamibi uptake in the myocardium is directly related to blood flow. In contrast to Tl-201, Tc-99m sestamibi has minimal or no myocardial redistribution. Tc-99m sestamibi can be injected at the bedside, in the exercise laboratory or in the catheterization room, and the imaging can be performed several hours later in the nuclear medicine department.

We performed 2 studies to assess the value of Tc-99m sestamibi in the catheterization laboratory. First, we investigated whether Tc-99m sestamibi imaging could demonstrate the area of the myocardium at risk during short episodes of severe ischemia. Intravenous injections of Tc-99m-sestamibi were made during percutaneous transluminal coronary angioplasty (PTCA) in patients with 1-vessel coronary disease, and imaging was performed after catheterization. In a second study, we determined whether selective intracoronary injection of Tc-99m sestamibi would demonstrate the size of the myocardial area perfused by that artery.

METHODS

Study 1: percutaneous transluminal coronary angiography and use of technetium-99m sestamibi: We studied 9 men and 4 women ranging from 38 to 71 years of age (mean 58 ± 7). Eleven patients had stable anginal complaints (class II to III according to the New York Heart Association classification) despite medical treatment with β -blocking agents, long-acting nitroglycerin and calcium antagonists. Two patients were admitted with unstable angina and treated with intravenous nitroglycerin, calcium antagonists and β -blocking agents. None of the patients had a previous myocardial infarction. All had normal resting electrocardiograms and normal left ventricular contraction patterns during cineangiography. In addition all had 1-vessel coronary disease, where the lumen diameter was narrowed $\geq 75\%$.

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TABLE I Clinical, Angiographic, I	Electrocardiographic and						
Scintigraphic Manifestations							

Country of the									
	Diseased	Collat-	Occlu-	_	ECG	Defeat			
Pt	Vessel	erals	sion	Pain	Changes	Defect			
1	L	-	60	+	+	+			
2	L	_	30	+	+	+			
3	R		45	+	+	+			
4	L	_	60	+	+	+			
5	L	-	35	+	+	+			
6	C	-	60	-	+	+			
7	L	-	60	+	+	+			
8	R	1_	40	+	+	+			
9	C	_	60	+	+	+			
10	L		13	+	+	+			
11	L	_	30	+	+	+			
12	L	+	60	-	-	-			
13	C	+	60	-	-	-			
C =	= circumflex art	tery; ECG =	e ectrocardie y artery.	ographic;	L = left anterio	r descending			

Cardiac catheterization: We performed coronary angiography using the Judkin technique. We performed left coronary angiography in the 30° and 60° right anterior oblique projections and the 60° left anterior oblique projection. We made additional projections, including angulated views to demonstrate the stenosis, when indicated. We performed a right coronary angiogram in the 30° right anterior oblique and 60° left anterior oblique projections, with additional projections as necessary. Left ventricular angiograms were done in the 30° right anterior and 60° left anterior oblique projections. The angiograms were taken on 35 mm cine film exposed at 60 frames/s with a Siemens U system cardioscope (Siemens AG). At least 2 observers interpreted coronary angiograms and ventriculograms.

When a stenosis was judged suitable for PTCA, the coronary angiogram was repeated in the projection in which the stenosis was best seen after heparinization. After the balloon was initially inflated, 20 mCi of Tc-99m sestamibi was immediately injected intravenously in an arm vein. During the PTCA procedure, patients were continuously monitored with an electrocardiogram using 6 simultaneous surface leads. The first balloon inflation lasted 60 seconds, or less if the patient experienced severe chest pain or ST-segment depression ≥4 mm in >2 leads.

Single photon emission computed tomography acquisition and processing: After completion of the balloon dilatation and at least 1 hour after the injection of Tc-99m sestamibi, the patient was brought to the nuclear medicine laboratory for imaging. Single photon emission computed tomography (SPECT) acquisition was performed with a Technicare Gemini camera (Technicare Corporation) with a low-energy, all-purpose, parallelhole collimator. Thirty projections (60 seconds each) were obtained over a 180° arch extending from the 45° left posterior oblique to the right anterior oblique position. A 20% symmetric energy window centered in the 140 keV peak was used. All data were stored on the hard

disk of a 560 Technicare mobile computer (Technicare Corporation) using a 64 × 64 word-mode matrix.

Processing: For nonuniformity correction, a Tc-99m flood source was counted weekly, accumulating 400 million counts. We determined the mechanical center of rotation from the projection data to align the detector data with respect to the reconstruction matrix. The raw data were initially smoothed with a 9-point weighted average algorithm.

Filtered back-projection was then accomplished using a low-resolution Butterworth filter with a cutoff frequency of 0.5 cycles/pixel order 5, to reconstruct transverse axial tomograms of 12.4 mm thickness/slice, encompassing the entire heart. Sagittal and oblique tomograms parallel to the long and short axis of the left ventricle were then extracted from the filtered transaxial tomograms by performing a coordinate transformation with the appropriate interpolation.13 For attenuation correction, we used a linear coefficient of 0.12. For visual interpretation, all short-axis and horizontal long-axis tomograms were displayed on transparent film.

Study 2: use of technetium-99m sestamibi to determine selected coronary artery perfusion: We studied 11 men and 4 women between 31 and 73 (mean 51 ± 9) years of age. Six patients had documented rhythm disturbances, and 9 patients were considered to have anginal complaints, class II to class III, according to the New York Heart Association classification system.

No patient had a previous myocardial infarction. All had normal resting electrocardiograms and normal left ventricular contraction patterns during cineangiography. We performed cardiac catheterization as described previously. For 7 patients, 1 mCi of Tc-99m sestamibi was injected into the proximal portion of a normal right coronary artery; for 4 patients 1 mCi of Tc-99m sestamibi was injected into the left anterior descending coronary artery just after its origin from the left main coronary artery; and for 2 patients, 1 mCi of Tc-99m sestamibi was injected into the proximal portion of a normal circumflex coronary artery. In 1 patient, a specially developed catheter was used to inject the radioactive tracer into the first septal branch. In another, a specially developed catheter was used to inject the radioactive tracer into the atrioventricular nodal branch of the right coronary artery.

Nuclear imaging: After catheterization, patients were brought to the nuclear medicine laboratory for imaging. For all studies, we used a mobile Technicare gamma camera (Technicare Corporation) with an all-purpose, parallel-hole collimator interfaced to a Technicare 560 mobile computer system. In all patients, we recorded 3 views: 45° left anterior oblique, anterior and left lateral, using a preset time of 360 seconds. The window was 20% with a photopeak of 140 keV.

RESULTS

Study 1: We successfully performed a PTCA procedure in the left anterior descending coronary artery in 8 patients (Table I). In 2 patients, we successfully per-

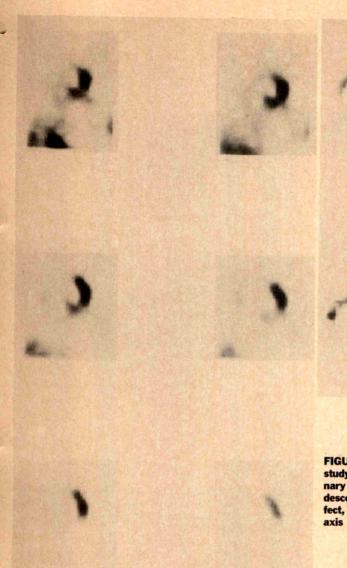




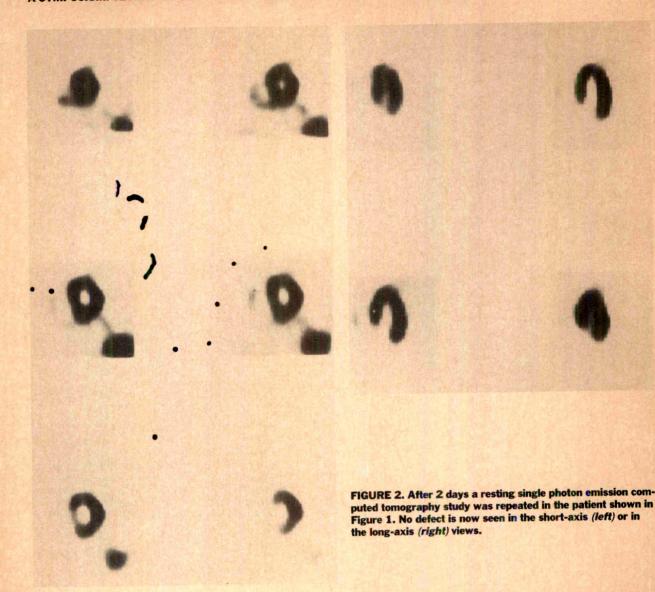
FIGURE 1. A single photon emission computed tomography study of a patient in whom a percutaneous transluminal coronary angioplasty procedure was performed in the left anterior descending coronary artery. Note the large anteroseptal defect, which is seen as well in the short axis (left) as in the long axis (right).

formed PTCA in the right coronary artery, and in 3 patients we successfully performed PTCA in the circumflex coronary artery. The occlusion time varied between 13 and 60 (mean 47) seconds. In 11 patients, electrocardiographic changes or chest pain, or both, occurred during the balloon inflation. In the 2 patients admitted with unstable angina and treated with intravenous nitroglycerin, no electrocardiographic changes or chest pain occurred. One of these patients had a subtotal stenosis of the left anterior descending coronary artery and the other had a subtotal stenosis of the circumflex artery. In both of these patients good collateral circulation was present.

After PTCA, there were no enzyme increases or electrocardiographic changes suggestive of acute myocardial infarction in any patient. In the 11 patients who developed chest pain and electrocardiographic changes during balloon occlusion, a perfusion defect on SPECT imaging was present (Fig. 1) and its location corresponded to the vessel in which the PTCA procedure was performed. Also, the size of the defect correlated with the site of

stenosis, with the largest defects seen in proximal stenoses. The SPECT images of the 2 patients with collateral vessels, who had no chest pain or electrocardiographic changes during PTCA, showed no defects. In 5 patients, SPECT imaging repeated 2 days after the PTCA procedure demonstrated no defects (Fig. 2).

Study 2: Angiography results showed that 8 patients had normal coronary arteries, 5 patients had 3-vessel disease and 2 patients had 2-vessel disease (right coronary artery and left anterior descending coronary artery). None of the 15 patients experienced any side effects from Tc-99m sestamibi. In all patients radioactive uptake was found in the myocardium, and in all cases the uptake corresponded to the flow area of the coronary artery in which Tc-99m sestamibi was selectively injected. In 7 patients in whom Tc-99m sestamibi was injected in the right coronary artery, uptake varied. In a large right coronary artery, we visualized the right ventricle, the inferior and posterior walls of the left ventricle and a part of the interventricular septum, while in a small nondom-



inant right coronary artery only the right ventricle was seen. In the other 5 patients, results varied between these 2 pictures. In the 4 patients in whom Tc-99m sestamibi was injected in the left anterior descending coronary artery, the results varied as well. In all patients, the interventricular septum showed uptake of the tracer, but the uptake of the anterior wall varied. In 1 patient, in addition to the septum and the anterior wall, we also visualized a large part of the inferior wall. This patient had a large left anterior descending coronary artery, which supplied a part of the inferior wall of the left ventricle. In the other 2 cases of selective peripheral septal and atrioventricular nodal injections, the distribution territory was clearly smaller compared to the proximal injections.

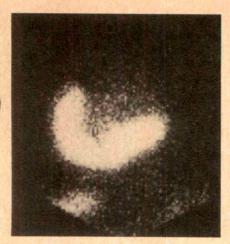
The target-to-background ratio was very high (Fig. 3) because no, or only minimal, activity was seen outside the flow area of the selectively injected coronary artery.

DISCUSSION

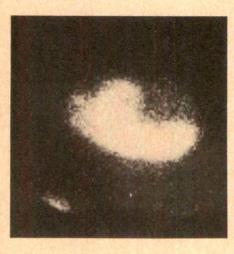
Our study shows that Tc-99m sestamibi can detect short episodes of ischemia and demonstrate the flow area of the individual coronary arteries, without the need to scan the patient immediately after injection of the radioactive tracer. Documentation of the ischemic area during short episodes of ischemia, with or without electrocardiographic changes, is of obvious diagnostic value. For example, a patient can be injected during an episode of pain, and after the patient is stabilized, imaging can be performed to identify areas of myocardial ischemia and to estimate the size of the jeopardized myocardium. This approach may also allow better evaluation of the effect of thrombolytic therapy in patients admitted with an acute myocardial infarction. ¹⁴ By using Tc-99m sestamibi in sequential studies, it might become possible to judge individually the extent of ischemia and how much myocardium was salvaged. The amount of salvage could influence the treatment strategy.

Our study also suggests the importance of collateral coronary circulation. Two patients admitted with unstable angina who had significant electrocardiographic changes later stabilized after medical treatment (showing normalization of the electrocardiogram). During injection of contrast into the right coronary artery, abundant collateral circulation to the left system was seen, and both

LAO



ANT



LL

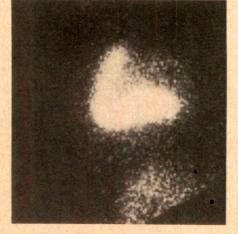


FIGURE 3. Three planar views after selective injection of technetium-99m sestamibi in a dominant right coronary artery. The left anterior oblique (LAO) view shows the right ventricle and the inferior wall of the left ventricle. The anterior (ANT) view shows the anterior wall of the right ventricle and the inferior wall of the left ventricle. The left lateral (LL) view shows the anterior wall of the right ventricle and the posterior wall of the left ventricle.

patients experienced chest pain. In both, no chest pain or electrocardiographic changes occurred during balloon inflation of the severely narrowed coronary artery, and the SPECT imaging showed no defects.

The visualization of the area of perfusion by the individual coronary artery helps us to understand the planar images obtained after an exercise test. After visualization of the flow areas of 7 right coronary arteries, of which 5 were dominant, we understand much better the differences in the size of defects that can be seen in patients with a proximal stenosis of the right opronary artery. The right coronary artery cannot only e dominant, but also the blood supply to the inferior part of the interventricular septum and the posterior wall of the left ventricle may vary considerably. The blood supply of the left anterior descending artery can also vart. In 3 of the 4 patients in this series, the blood supply represented by the Tc-99m sestamibi uptake covered the anterolateral wall, making it understandable that the sensitivity for detection of lesions in the circumflex coronary artery is low. A limitation of intracoronary administration of radionuclides can be streaming after injection, which can lead to preferential uptake through 1 of the branches of the coronary vessel rather than homogeneous distribution throughout the entire risk area.

Selective coronary artery injection of Tc-99m sestamibi not only allows better understanding and interpretation of planar images, but potentially its use might also differentiate between viable and necrotic myocardium. ¹⁵ If a patient has suffered an acute myocardial infarction, it is not always easy to predict whether PTCA or bypass of the infarct-related vessel will be of value. If, after selective injection of Tc-99m sestamibi in the infarct-related artery, a large area of radioactive uptake is seen on the images, PTCA or bypass of that vessel would seem reasonable. This technique can also be used to predict the area of jeopardized myocardium after occlusion at a specific place in the coronary artery.

Recently, in some of our patients in whom conventional treatment failed to control ventricular rhythm disturbances, we used selective alcohol injection to destroy the area in which the tachycardia originated. We believe that Tc-99m sestamibi also allows estimation of the area perfused by the artery considered to be supplying the arrhythmogenic area. Careful estimation of the size of that area will prevent destruction of excess myocardial tissue.

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A SYMPOSIUM: TECHNETIUM-99m IMAGING AGENTS

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Technetium-99m Sestamibi in Chronic Coronary Artery Disease: The European Experience

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Since the introduction of technetium-99m methoxy-isobutyl isonitrile (Tc-99m sestamibi) in Europe, there has been a growing interest in its use. Several European multicenter trials have been conducted to evaluate this new agent in relation to the traditional perfusion marker thallium-201, and other studies are in progress to understand the use of this perfusion marker for the diagnosis of coronary disease, for use in conjunction with pharmacologic vasodilation, for use in the assessment of ventricular function and wall motion and for the assessment of interventions.

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hallium-201 (Tl-201) has been the traditional "workhorse" for myocardial perfusion imaging for more than a decade and has been widely accepted and applied. However, due to the suboptimal physical characteristics of Tl-201, the introduction of technetium-99m (Tc-99m)-labeled radiopharmaceuticals has been considered a major breakthrough for myocardial scintigraphy. 1-3 The compound Tc-99m sestamibi (Tc-99m methoxy-isobutyl isonitrile) has exhibited a favorable spectrum of properties including minimal redistribution, a high extraction fraction as a perfusion marker and high photon flux due to the Tc-99m label. Tc-99m sestamibi has been introduced into large clinical trials in the United States, Canada and Europe. More recently it has become available either on a prescription basis or for commercial sale in several European countries.

Based on its physical and biologic characteristics, Tc-99m sestamibi is expected to offer several advantages, such as improved single photon emission computed to-mography (SPECT),⁴ simultaneous evaluation of ventricular function and myocardial perfusion with 1 radio-tracer, and assessment of interventions.^{5,6} We summarize the most important European experiences with Tc-99m sestamibi, with special emphasis on applications in chronic coronary artery disease (CAD).

Since the introduction of Tc-99m sestamibi in Europe, there has been a growing interest in its use. Several European multicenter trials have been conducted, and other studies are under way investigating the use of Tc-99m sestamibi in comparison with Tl-201 in chronic CAD and myocardial infarction, and confirming its use in determining first-pass ventricular function. In addition, several European groups have used this new perfusion tracer on a broader clinical basis or have conducted special targeted studies.

TECHNETIUM-99m SESTAMIBI AS A TRACER FOR SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY: EUROPEAN ACQUISITION PROTOCOLS AND RESULTS

One major area of interest regarding this new tracer has been its clinical utility and comparative value as an agent for SPECT. Karcher et al,8 from the French subgroup of the European Phase III Multicenter Study Trial, evaluating Tc-99m sestamibi in conjunction with stress testing for the diagnosis of ischemic cardiac disease, reported a study of 81 patients with proven CAD. They found a high concordance of abnormal segments for Tl-201 and Tc-99m sestamibi. Two independent observers interpreted both the Tl-201 SPECT and Tc-99m sestamibi SPECT studies. In cases of interobserver disagreement, a joint reading was made with a third observer to arrive at a consensus. The Tc-99m sestamibi studies were

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performed using a 370 MBq (10 mCi) injection at stress followed by a 740 MBq (20 mCi) injection at rest 6 hours later. The agreement between the 2 tracers was 89% (72 of 81 patients) for the left anterior descending artery as well as for the right coronary artery and the left circumflex artery. These investigators also reported interobserver agreement for Tl-201 and Tc-99m sestamibi. Comparing SPECT slices at rest and stress, 2 observers classified as abnormal or normal the territories supplied by the left anterior descending coronary artery, right coronary artery and left circumflex artery. Interobserver agreement for Tc-99m sestamibi was 95% for involvement of the left anterior descending coronary artery and 97% for the right coronary artery and left circumflex artery, whereas for Tl-201 values of 88% were found for the left anterior descending coronary artery and for the right coronary artery and left circumflex artery. These data suggest slightly improved interobserver agreement with Tc-99m sestamibi, possibly related to the improved image quality observed with this agent. However, because of the small number of patients, the differences did not reach statistical significance. These findings need further confirmation.

Other groups have concentrated on the feasibility of a 1-day protocol, as prolonged retention in the myocardium requires 2 separate injections, most commonly given on separate days. In clinical practice, however, a 1-day protocol would be desirable, offering improved logistics and the possibility for earlier decision making. In a selected series of 15 patients with angiographically proven CAD, Stirner et al9 compared Tl-201 and Tc-99m sestamibi using a same-day rest-exercise protocol and SPECT imaging. Using a dose of 240 MBq (6.5 mCi) of Tc-99m sestamibi at both exercise and rest with a 3-hour time difference between the 2 injections, a "net" rest distribution was obtained by subtracting the residual activity imaged just before the rest injection from the rest study. From polar, targetlike regions of interest, data were computed from short-axis cross-sectional slices, and regional values for uptake, washout and "washout corrected" redistribution were obtained. The investigators demonstrated high segmental agreement in 97% of the 60 myocardial segments evaluated. Using the resulting "net" rest distribution data, myocardial washout in the region of maximal myocardial activity was found to be $19 \pm 6\%$ for Tc-99m sestamibi and $42 \pm 7\%$ for Tl-201, whereas in the defect areas myocardial activity was 22 ± 12% for Tc-99m sestamibi and 25 ± 16% for Tl-201. These data suggest a 20% washout from both normal and abnormal areas with Tc-99m sestamibi. When quantifying the amount of fill-in of the defect (Tl-201 redistribution and reinjection of Tc-99m sestamibi, corrected for residual activity from the rest injection), the amount of change between postexercise data and rest data was not significantly different for the 2 tracers: 6.7 ± 10.2% for Tl-201 and 5.4 ± 5.9% for Tc-99m sestamibi in the area of maximal activity, and 36.1 ± 24.4% for Tl-201 and 39.8 ± 24.9% for Tc-99m sestamibi in the defect region. If uncorrected data (no subtraction of residual activity) were used for the calculation of the Tc-99m sestamibi

values, there was no difference between the amount of change in the region of maximal myocardial activity and that observed in the defect area: $9.8 \pm 6.5\%$ and $9.6 \pm$ 12.8%, respectively. Thus, the investigators concluded that Tl-201 and Tc-99m sestamibi resulted in almost identical myocardial defects both in size and amount of relative uptake when the residual activity from the first stress injection of Tc-99m sestamibi was subtracted from the rest study. The subtraction technique used in this study has inherent limitations, such as possible artifacts created by the algorithm and the necessity for the patient to remain in the same position between the exercise and rest study, which may preclude its use for routine clinical protocols.

In subsequent studies, 10,11 the same group further evaluated the possibilities of a 1-day protocol using 150 MBq (4 mCi) injected at exercise and 800 MBq (22 mCi) injected at rest in a 4-hour protocol. Exercise imaging was started 60 minutes after the injection. Immediately after image acquisition the rest injection was given, and images were obtained 2 hours later. One study in 70 patients with angiographically confirmed CAD and 10 control subjects11 described a semiquantitative index, the exerciserest ratio, or "perfusion reserve," as a correlate to coronary vascular reserve. This perfusion reserve is derived from global myocardial uptake (total left ventricle counts) and regional myocardial uptake of Tc-99m sestamibi on SPECT studies. The same segmentation approach from their previous study, 10 with targetlike representations of a series of short-axis slices corrected for decay, remaining activity and a "washout factor" of 20%, was used. These parameters were related to the degree of coronary artery stenosis by angiography. The investigators report the usefulness of "global and regional perfusion ratios" in quantitative Tc-99m sestamibi SPECT. However, one should be aware of the inherent inability to correct for differences in extraction fraction or metabolic influences, which in fact precludes the use of such ratios as direct equivalents for coronary perfusion reserve measurements. Nevertheless, these parameters successfully grouped myocardial areas for the severity of stenosis of the supplying vessel and separated abnormal subjects from control subjects sufficiently. Whether such an approach yields significant additional information in terms of diagnostic accuracy must be determined by further studies.

In the same study population, these investigators related the results of a quantitative analysis of the SPECT data to an evaluation of a perfusion index from myocardial uptake during exercise and rest. 10 The perfusion index during exercise and the perfusion index at rest are derived from the relative amount of Tc-99m sestamibi uptake in normalized to maximal activity within the perfusion map. These perfusion indices at exercise and rest were compared to qualitative visual readings of reversible, partially reversible and persistent defects (Table I). Sensitivity for CAD detection (stenosis >75%) by visual analysis of the SPECT images in this group of patients with a mean prevalence of disease of 72% was reported to be 96% (45 of 47) for patients and 89% for vessel assessment (56 of 63). This study also compared data from the 4-hour protocol with data from repeated rest injection after 24 hours in 10 patients and 21 defect areas (Table II). Perfusion indices in the defect areas at rest at 4 hours and after 24 hours were not different for reversible, partially reversible and persistent defects, suggesting the feasibility of a 4-hour (1-day) protocol and quantitative analysis to correctly assess the distribution and uptake patterns of Tc-99m sestamibi SPECT studies.

Taillefer et al, 12 using a short time interval (<2 hours) between 2 Tc-99m sestamibi injections, recently reported the superiority of a rest-stress sequence over a stress-rest sequence, applying qualitative analysis to the tomographic studies. In their study, 18 patients referred for chest pain underwent 2 complete Tc-99m sestamibi studies: a rest-stress study and a stress-rest study. For each Tc-99m sestamibi study, 4 presentations were available: a polar map and horizontal long-axis, vertical long-axis and short-axis slices. The left ventricle in each midplane was arbitrarily divided into 6 segments (18 segments/patient), which were scored to represent normal, ischemic or scar tissue, based on the presence of transient or fixed defects. A total of 324 segments were interpreted blindly by 3 observers. There was agreement in 283 of 324 (87.3%) segments in the 2 protocols. However, 24 segments (7.4%) were read as ischemic on the rest-stress sequence and as scar on the stress-rest sequence, which emphasizes the possible overestimation of persistent defects when a stress-rest sequence is used. In an earlier study,13 the same group demonstrated the feasibility and similar diagnostic information content of a longer 2-day protocol when the rest injection was done first, the stress injection second and a comparative stress study was obtained after 24 hours. These data resulted in identical numbers of ischemic and fixed defects and comparable normal-to-abnormal count ratios on same-day and 2-day protocols. Nonetheless, the problem of the resting radioactivity potentially masking exercise defects is acknowledged by the investigator. This study is discussed in greater detail by Taillefer elsewhere in this supplement.14

Several differences exist between the 2 approaches to a 1-day protocol. A summary of the 2 imaging protocols is shown in Figure 1. Taillefer et al¹² used 260 MBq (7 mCi) for the first injection and 925 MBq (25 mCi) for the second injection (activity ratio of exercise to rest of 1:3.6) and performed imaging 60 minutes after each injection with a single-head gamma camera. Buell et al10 injected 150 MBq (4.5 mCi) and 800 MBq (21.5 mCi) (activity ratio of exercise to rest of 1:5.3) and performed imaging 60 minutes after exercise but 120 minutes after the resting injection, allowing for more decay of the residual activity from the first injection. The latter study also included quantitative analysis; however, no crossover comparison of the imaging sequences (as in the Canadian study) was performed. Thus, it may be concluded that both protocols are feasible, offering high agreement of segmental readings and sensitivities well in the reported range for Tl-201 results and consistent with results of other studies.5 It should be noted, however, that if the stress study is performed first with a low dose of radioac-

TABLE I Comparison of Perfusion Index Studies During Exercise (PIE), Perfusion Index at Rest (PIR), and the Difference (Delta PI) with Visual Defect Type in 105 Vascular Supply Areas*

Parameter	Reversible (n = 34)		Partially Reversible (n = 36)		Fixed (n = 35)
PIE (%)	62.4 ± 9.2		46.1 ± 7.7	Miss Co.	33.5±9.9
		p < 0.01		p < 0.01	
Delta PI (%)	$+13.2 \pm 7.4$		$+10.1 \pm 6.5$		$+2.1 \pm 4.2$
		NS		€ <0.01	
PIR (%)	75.6 ± 7.5		56.2 ± 39	1	35.6±9.6
		p < 0.01		p < 0.01	

* All values mean ± standard deviation. Adapted with permission of Chapman (Hall, Ltd, publishers, from Buell et al. 10 NS = not significant.

TABLE II Comparison of Perfusion Index During Exercise (PIE), at Rest Using 4-Hour Protocol (PIR1) and at Rest After the Third Injection at 24 Hours (PIR2) with Visual Defect Type in 10 Patients*

Parameter (%)	Reversible	Partially Reversible	Fixed
PIE	50.0 ± 2.5	40.3 ± 2.6	32.1 ± 3.7
PIR1	75.3 ± 3.5	60.3 ± 5.2	34.8 ± 3.5
PIR2	70.3 ± 4.6	64.0 ± 4.8	30.8 ± 3.4

Taillefer
260 MBq
(7 mCi)
stress injection

0 60 90 100 150

Time (minutes)

Buell
150 MBq
(4.5 mCi)
stress injection

150 min
simaging

120 min
simaging
si

FIGURE 1. Comparative exercise-rest 1-day protocols.

tivity, accurate exercise ejection fraction measurements from the first pass may not be possible. In addition, the stress images may have a low count density, reducing image quality for this most important exercise defect analysis. Therefore, it seems that the imaging protocol used may be related to the diagnostic question asked and the logistics and scheduling requirements of the imaging department.

TECHNETIUM-99m SESTAMIBI AND ASSESSMENT OF VENTRICULAR FUNCTION BY GATED PLANAR AND TOMOGRAPHIC TECHNIQUES

Data exist from various groups in Europe studying simultaneous assessment of regional wall motion and per-

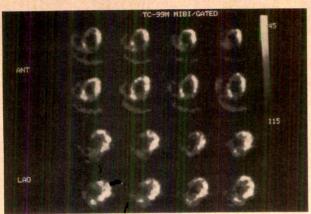


FIGURE 2. Multiple gated technetium-99m (Tc-99m) sestamibi study (top, anterior view; bottom, 70° left anterior oblique [LAO] view) in a patient with anterior (ANT) myocardial infarction. The ANT well and the apex exhibit clear perfusion defects. The anterolateral wall shows preserved thickening as well as the normal inferior segments. MIBI = sestamibi.

fusion with gated planar and SPECT studies. 15-19 In a planar imaging study of 62 patients, Najm et al15 calculated the radionuclide fractional shortening from the anteroposterior wall axis and the septum to the lateral wall axis in diastole and systole and compared the results with the echocardiographic fractional shortening measurements. The radionuclide fractional shortening in the anteroposterior axis correlated closely with echocardiographic fractional shortening (r = 0.89, p < 0.001). This study is discussed in detail in the report by Maisey et al²⁰ in this supplement.

Marcassa et al16 studied 10 normal volunteers to develop a method for quantitating left ventricular (LV) regional wall thickening by gated Tc-99m sestamibi studies and to assess the pattern of regional LV wall thickening. Echocardiography, performed in multiple views to evaluate all myocardial regions, showed normal ventricular function in all subjects. Gated radionuclide perfusion stadies (16 frames/R-R interval) were obtained at rest 60 to 90 minutes after an injection of 740 MBq (20 mCi) of Tc-99m sestamibi. Regional systolic thickening profiles were calculated along 60 radii, averaged to 12 segmental values, of the end-diastolic and end-systolic frames according to the forumula: (end-systolic count profile end-diastolic count profile)/(end-diastolic count profile + background) × 100.

The values of systolic thickening were recalculated in all subjects by the same observer on 2 occasions at least 1 week apart and also by a second observer. The intra- and interobserver variability in thickening measurements was ±5.4 and ±4.1%, respectively. Their data on the pattern of LV regional wall thickening in normal subejcts were similar to echocardiographic results, as well as data obtained from cine computed tomography and nuclear magnetic resonance imaging.

In an earlier study of 10 patients with myocardial infarction, Clausen et al17 compared a "contraction fraction," obtained by determining the fractional increase of

the LV systolic count density in relation to diastolic count density on gated planar studies, with gated blood pool regional ejection fraction values and with relative infarct size measured by SPECT perfusion defects. The investigators found correlation coefficients of 0.87 and 0.93, respectively. More studies are needed before the role of planar gated perfusion imaging using Tc-99m sestamibi can be fully assessed, as there are several limitations to this methodology, including reduced count rates in the areas of perfusion defects and difficulty in delineating inner and outer borders of the myocardium. Functional count-based data, however, or a combination with amplitude analysis derived from Fourier analysis, may offer possible solutions for improved assessment.

Several groups have also successfully used gated SPECT techniques for the assessment of ventricular function. In a preliminary study, we reported comparative data from echocardiography in 3 standard orientations and planar or gated, or both, SPECT Tc-99m sestamibi studies in 36 patients. 18 Patient examples are shown in Figures 2 and 3. Applying a semiquantitative wall motion score for both modalities, correlations were r = 0.759 for planar imaging and r = 0.855 for gated SPECT. Figure 4 shows the total correlation between echocardiographic assessment and Tc-99m sestamibiderived functional scores with a correlation coefficient of r = 0.805. Imaging protocols in this study included 3view gated planar studies using 16 frames/cycle after an injection of 185 to 370 MBq (5 to 10 mCi) of Tc-99m sestamibi or injection of 555 to 740 MBq (15 to 20 mCi) of Tc-99m sestamibi and reconstruction of 3 SPECT orientations using a 180° step and shoot gated SPECT acquisition and 18 frames/cycle condensed to 8 frames/ cycle for better visual analysis.

Thus, several preliminary studies have demonstrated that Tc-99m sestamibi perfusion information provides high-quality myocardial images with adequate counting statistics to retrieve wall motion information. However, this approach to regional function assessment may have limitations in low-count areas, particularly if only visual

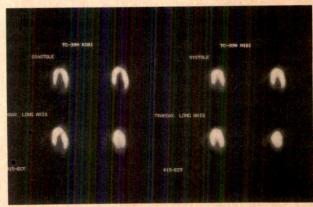


FIGURE 3. Normal gated single photon emission computed tomography study: consecutive end-diastolic (left) and end-systolic (right) slices in horizontal long-axis orientation. Note normal thickening and homogeneous perfusion. Transax. = transaxial; other abbreviations as in Figure 2.

analysis is used. In addition, it is also possible to obtain high-quality first-pass functional data, especially with dedicated multicrystal instrumentation.

Larock et al19 investigated the incremental information obtained from gated SPECT compared to standard nongated SPECT data. By comparison of diastolic and systolic frames, gated tomography offers the potential for the analysis of wall motion and wall thickening in combination with high-contrast perfusion information. This might be especially useful in areas of normal or only slightly reduced perfusion with impaired function, or in areas where a perfusion defect has been "frozen" (during exercise or spontaneous chest pain, after an intervention such as percutaneous transluminal coronary angioplasty or before thrombolysis), and can be related to the functional status at a later time. In this scenario, the ability to separate the time of imaging from the time of injection may be an additional advantage. These tracer characteristics have been shown to be especially important for the early assessment of salvaged myocardium and prediction of late functional recovery, as reported by several European groups. 21,22

In addition, Philippe et al²³ explored the possibility of gated Tc-99m sestamibi SPECT data for LV volume assessment in comparison to contrast ventriculography. An excellent correlation was obtained between the angiographic results and those obtained from end-diastolic and end-systolic measurements from the gated SPECT perfusion images (r = 0.93). Grucker et al²⁴ used contraction information derived from 60 radial vectors of 2 "thick" short-axis slices in each phase of the cardiac cycle, obtaining regional time-activity-like cuves. This approach allows for potentially more accurate sizing of the injured myocardium because there is no averaging between systolic and diastolic activity as with Tl-201 scintigraphy.

TECHNETIUM-99m SESTAMIBI IN DOUBLE TRACER STUDIES

Knapp et al25 have reported initial experiences with simultaneous dual isotope planar studies using indium-111 antimyosin for the demarcation of necrosis and Tc-99m sestamibi for demarcation of the hypoperfused zone. The Tc-99m sestamibi images were acquired in a multigated mode to provide information on both wall motion and perfusion. The combined use of the indium-111 antimyosin antibody and gated Tc-99m sestamibi imaging may allow distinction of stunned, hypoperfused and viable, and hypoperfused but nonviable zones. Similar to the Tl-201-indium-111 antimyosin data outlined by Johnson et al,26 patients with "mismatch" territories (areas with larger perfusion defects than determined by antimyosin uptake or in remote segments) more frequently had future ischemic events than did those with matched defects (perfusion defects equal in size to the region of antimyosin uptake).

SUMMARY

Since the introduction of Tc-99m sestamibi in Europe, a variety of institutions have gathered a considerable amount of experience in a large number of patients. Data

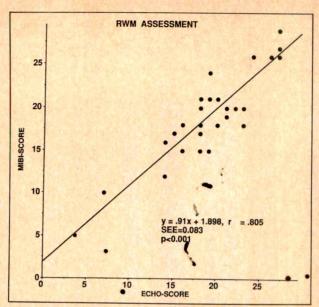


FIGURE 4. Correlation of comparative ventricular function assessment by gated technetium-99m sestamibi score (y axis) and semiquantitative echo score (as a sum of segmental scoring for 3 echocardiographic orientations) demonstrates good agreement. RWM = regional wall motion; SEE = standard error of the estimate; other abbreviations as in Figure 2.

from centers participating in the multicenter clinical trials as well as more targeted studies indicate a whole spectrum of improvements and new possibilities for myocardial perfusion imaging with Tc-99m sestamibi. Several factors, however, are likely to influence the possible routine use of Tc-99m sestamibi and eventual replacement of Tl-201. More extensive studies are needed in different patient populations to verify the accuracy of this agent in a variety of clinical settings. Further studies are also required to determine optimal imaging protocols relative to clinical needs, develop quantification programs (requiring a normal database) and devise appropriate background subtraction algorithms. Ongoing clinical trials involving comparisons between Tl-201 and Tc-99m sestamibi using intravenous dipyridamole as a stress method must be completed to determine the clinical utility and efficacy of this pharmacologic stress test with this new tracer.

The introduction of Tc-99m sestamibi has stimulated extensive work in a variety of institutions worldwide. Further studies from multiple institutions will soon enhance our present knowledge about the capability of this new imaging tracer, and are likely to give new emphasis and importance to the application of cardiovascular nuclear medicine procedures in general and perfusion imaging in particular.

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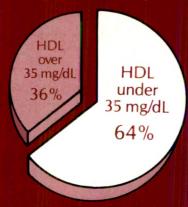




What's a common denominator of most heart attack victims?

Mixed hyperlipidemias—elevated cholesterol and triglycerides—are common among heart attack victims,¹ and nearly two-thirds of people who developed myocardial infarction in the PROCAM Trial had a low (<35 mg/dL) baseline level of HDL cholesterol.²

HEART ATTACK PATIENTS (PROCAM TRIAL)²



A powerful case for [OPD] BID BID (gemfibrozil) 600-mg Tablets

Raised low HDL 25%

—in patients whose baseline HDL was below 35 mg/dL in the landmark Helsinki Heart Study (HHS).3

Reduced heart attack incidence* up to 62%

—in these HHS patients and 45% in HHS patients whose baseline HDL was below the median (46.4 mg/dL). Incidence of serious coronary events was similar for LOPID and placebo subgroups with baseline HDL above the median (46.4 mg/dL).

Raised HDL levels 1½ to 3 times more effectively than lovastatin

—in a 12-week, double-blind, randomized trial among patients with moderate to severe hyperlipidemia. Lovastatin achieved greater reductions in total serum cholesterol than gemfibrozil in this study population.⁴

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LOPID is indicated for reducing the risk of coronary heart disease (CHD) in Type IIb patients with low HDL, in addition to elevated LDL and triglycerides, and who have had an inadequate response to weight loss, diet, exercise, and other pharmacologic agents such as bile acid sequestrants and nicotinic acid.

*Defined as a combination of definite coronary death and/or definite myocardial infarction.

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Please see last page of this advertisement for warnings, contraindications, and brief summary of prescribing information.

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Before prescribing, please see full prescribing information. A Brief Summary follows.

CONTRAINDICATIONS. 1. Hepatic or severe renal dysfunction, including primary iliary cirrhosis

2. Preexisting gallbladder disease (See WARNINGS)

3. Hypersensitivity to gemfibrozil.

WARNINGS. 1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects. developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization (WHO), 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant, 29%, higher total mortality in the clofibrate-treated than in a comparable placebo-treated control group. The excess mortality was due to a 33% increase in noncardiovascular causes, including malignancy, postcholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

subjects for gallbladder disease was confirmed.

During the Helsinki Heart Study and in the 1½ year follow-up period since the trial was completed, mortality from any cause was 59 (2.9%) in the Lopid group and 55 (2.7%) in the placebo group. Mortality from any cause during the double-blind portion of the study was 44 deaths in the Lopid group and 43 in the placebo group. Because of the more limited size of the Helsinki Heart Study, this result is not statistically-significantly clifferent from the 29% excess mortality seen in the clofibrate group in the separate WHO study. Noncoronary heart disease related mortality showed a 58% greater trend in the Lopid group (43 vs 27 patients in the placebo group, p=0.056). In the Helsinki Heart Study, the incidence of total malignancies discovered during the

In the Heisinki Heart Study, the incidence of total manignancies discovered during the trial and in the 1½ years since the trial was completed was 39 in the Lopid group and 29 in the placebo group (difference not statistically significant). This includes 5 basal cell carcinomas in the Lopid group and none in the placebo group (p=0.06; historical data predicted an expected 4.7 cases in the placebo group). Gl malignancies and deaths from malignancies were not statistically different between Lopid and placebo subservers. Explanate the Meliniki Heart

groups. Follow-up of the Helsinki Heart Study participants will provide further infor-mation on cause-specific mortality and

cancer morbidity.

2. A gallstone prevalence substudy of 450 Helsinki Heart Study participants showed a trend toward a greater prevalence of gall-stones during the study within the Lopid treatment group (7.5% vs 4.9% for the place bo group, a 55% excess for the gemfibrozil group). A trend toward a greater incidence of gallbladder surgery was observed for the Lopid group (17 vs 11 subjects, a 54% ex-cess). This result did not differ statistically

cess). This result did not differ statistically from the increased incidence of cholecystectomy observed in the WHO study in the group treated with clofibrate. Both clofibrate and gemfibrozil may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Lopid therapy should be discontinued if gallstones are found.

 Since a reduction of mortality from coronary artery disease has not been demonstrated and because liver and interstitial cell testicular tumors were increased in rats, Lopid should be administered only to those patients described in the INDICATIONS AND USAGE section. If a significant serum lipid response is not obtained, Lopid should be discontinued.

4. Concomitant Anticoagulants — Caution should be exercised when anticoagulants are given in conjunction with Lopid. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined

that the prothrombin level has stabilized.

5. Concomitant therapy with Lopid and Mevacor® (lovastatin) has been associated with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure (See Drug Interactions). The use of fibrates alone, including Lopid, may occasionally be associated with myositis. Patients receiving Lopid and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myositis, including serum creatine kinase level determination. If myositis is suspected or diagnosed, Lopid therapy should be withdrawn.

6. Cataracts—Subcapsular bilateral cataracts occurred in 10%, and unilateral in 63% of male rats treated with gernfibrozil at 10 times the human dose.

PRECAUTIONS. 1. Initial Therapy — Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal. Before instituting Lopid therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control serum lipids with appropriate disc, exercise, weight odd in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities.

2. Continued Therapy — Periodic determination of serum lipids should be obtained, and the drug withdrawn if lipid response is inadequate after 3 months of therapy.

3. Drug Interactions — (A) Lovastatin: Rhabdomyolysis has occurred with combined the description of the property of the pr

gemfibrozil and lovastatin therapy. It may be seen as early as 3 weeks after initiation of combined therapy or after several months. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhab-domyolysis, and acute renal failure. There is no assurance that periodic monitoring of

domyolysis, and acute renal tailure. There is no assurance that periodic monitoring of creatine kinase will prevent the occurrence of severe myopathy and kidney damage. (B) Anticoagulants: CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

DEFINITELY DETERMINED THAT THE PHOTHROMBIN LEVEL THAS STABILIZED.

4. Carcinogenesis, Mutagenesis, Impairment of Fertility—Long-term studies have been conducted in rats and mice at one and ten times the human dose. The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant (p=0.1). In high dose female rats, there was a significant increase in the combined incidence of benign, and malignant liver was a significant to produce the rate of the production of the producti neoplasms. In male and female mice, there were no statistically significant differences

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from controls in the incidence of liver tumors, but the doses tested were lower than those shown to be carcinogenic with other fibrates

Male rats had a dose-related and statistically significant increase of benign Leydig ce tumors at 1 and 10 times the human dose.

Electron microscopy studies have demonstrated a florid hepatic peroxisome prolifera tion following Lopid administration to the male rat. An adequate study to test for peroxisome proliferation has not been done in humans but changes in peroxisome morphology have been observed. Peroxisome proliferation has been shown to occur in humans with either of two other drugs of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Administration of approximately three or ten times the human dose to male rats for 10 weel resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that the effect was reversed after a drug-free period of about eight weeks, and it was not transmi

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ted to the offspring.

5. Pregnancy Category B – Reproduction studies have been performed in the rat at 5. Pregnancy Category B – Reproduction studies have been performed in the rat at 5. Pregnancy Category B – Reproduction studies have been performed in the rat at 5. Pregnancy Category B – Reproduction studies have been performed in the rat at 5. Pregnancy Category B – Reproduction studies have been performed in the rat at 5. Pregnancy Category B – Reproduction studies have been performed in the rat at 5. Pregnancy Category B – Reproduction studies have been performed in the rat at 5. Pregnancy Category B – Reproduction studies have been performed in the rat at 5. Pregnancy Category B – Reproduction studies have been performed in the rat at 6. Pregnancy Category B – Reproduction studies have been performed in the rat at 6. Pregnancy Category B – Reproduction studies have been performed in the rat at 6. Pregnancy Category B – Reproduction studies have been performed in the rat at 6. Pregnancy Category B – Reproduction studies have been performed in the rat at 6. Pregnancy Category B – Reproduction studies have been performed in the rate of 6. Pregnancy Category B – Reproduction studies have been performed in the rate of 6. Pregnancy Category B – Reproduction studies have been performed in the rate of 6. Pregnancy Category B – Reproduction studies have been performed by 6. Pregnancy Category B – Reproduction studies have been performed by 6. Pregnancy Category B – Reproduction studies have been performed by 6. Pregnancy B – Reproduction studies have been performed by 6. Pregnancy B – Reproduction studies have been performed by 6. Pregnancy B – Reproduction studies have been performed by 6. Pregnancy B – Reproduction studies have been performed by 6. Pregnancy B – Reproduction studies have been performed by 6. Pregnancy B – Reproduction studies have been performed by 6. Pregnancy B – Reproduction studies have been performed by 6. Pregnancy B – Reproduction studies have been performed by 6. Pregnancy B – Reproduct doses 3 and 9 times the human dose, and in the rabbit at 2 and 6.7 times the human dose. These studies have revealed no evidence of impaired fertility in females or harm to the fetus due to Lopid. Minor fetotoxicity was manifested by reduced birth rates observe

the fetus due to Lopid. Minor fetotoxicity was manifested by reduced birth rates observe at the high dose levels. No significant malformations were found among almost 400 offspring from 36 litters of rats and 100 fetuses from 22 litters of rabbits.

There are no studies in pregnant women. In view of the fact that Lopid is tumorigenic male and female rats, the use of Lopid in pregnancy should be reserved for those patients where the benefit clearly outweighs the possible risk to the patient or fetus.

6. Nursing Mothers — Because of the potential for tumorigenicity shown for gemfibrozil in rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

7. Hematologic Changes — Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of Lopid therapy. However, these levels stabilize during long-term administration. Rarely, severe anemia, leukopenia, thrombocytopenia, and bone marrow hypoplasia have been anemia, leukopenia, thrombocytopenia, and bone marrow hypoplasia have been reported. Therefore, periodic blood counts are recommended during the first 12 month of Lopid administration.

8. Liver Function — Abnormal liver function tests have been observed occasionally during Lopid administration, including elevations of AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase. These are usually reversible when Lopid is discontinued. Therefore periodic liver function studies are recommended and Lopid there

should be terminated if abnormalities persi 9. **Use in Children** – Safety and efficacy children have not been established. ADVERSE REACTIONS. In the double-blir controlled phase of the Helsinki Heart Stud 2046 patients received Lopid for up to 5 year In that study, the following adverse reaction were statistically more frequent in subjects the Lopid group (placebo incidence in pare

theses): gastrointestinal reactions, 34.2% (23.8%); dyspepsia, 19.6% (11.9%); abdominal pain, 9.8% (5.6%); acute appendicitis (histologically confirmed in most cases where data are available), 1.2% (0.6%); atrial fibrillation, 0.7% (0.1%)

fibrillation, 0.7% (0.1%).

Adverse events reported by more than 1% of subjects, but without a significant difference between groups (placebo incidence in parentheses) were: diarrhea, 7.2% (6.5% fatigue, 3.8% (3.5%); nausea/vomiting, 2.5% (2.1%); eczema, 1.9% (1.2%); rash, 1.7% (1.3%); vertigo, 1.5% (1.3%); constipation, 1.4% (1.3%); headache, 1.2% (1.1%). Gallbladder surgery was performed in 0.9% of Lopid and 0.5% of placebo subjects, 64% excess, which is not statistically different from the excess of gallbladder surgery observed in the clofibrate compared to the placebo group of the WHO study.

Nervous system and special senses adverse reactions were more common in the Lopid group. These included hypesthesia, paresthesias, and taste perversion. Other adverse reactions that were more common among Lopid treatment group subjects but where a causal relationship was not established include cataracts, peripheral vascular

where a causal relationship was not established include cataracts, peripheral vascular disease, and intracerebial hemorrhage.

From other studies it seems probable that Lopid is causally related to the occurrence of musculoskeletal symptoms (See WARNINGS), and to abnormal liver function tests and hematologic changes (See PRECAUTIONS).

Reports of viral and bacterial infections (common cold, cough, urinary tract infections) we more common in gemfibrozil-treated patients in other controlled clinical trials of 805 patier. Additional adverse reactions that have been reported for gemfibrozil are listed below.

by system. These are categorized according to whether a causal relationship to treatment with Lopid is probable or not established:

CAUSAL RELATIONSHIP PROBABLE: Gastrointestinal: cholestatic jaundice; Central CAUSAL RELATIONSHIP PROBABLE: Gastromessimal: cholestatic jauniatie, Central Nervous System: dizziness, somnolence, paresthesia, peripheral neuritis, decreased libido, depression, headache; Eye: blurred vision; Genitourinary: impotence; Musculoskeletal: myopathy, myasthenia, myalgia, painful extremities, arthralgia, synovitis, rhabdomyolysis (see WARNINGS and Drug Interactions under PRECAUTIONS); Clinical Laboratory: increased creatine phosphokinase, increased bilirubin, in creased liver transaminases (AST [SGOT], ALT [SGPT]), increased alkaline phosphatas Hematopoietic: anemia, leukopenia, bone marrow hypoplasia, eosinophilia; Imposed alicence increased letterage adequate articipatic intergramentary; exfoliative dermunologic: angioedema, laryngeal edema, urticaria; Integumentary: exfoliative dermatitis, rash, dermatitis, pruritus.
CAUSAL RELATIONSHIP NOT ESTABLISHED: General: weight loss; Cardiac: extrasy

CAUSAL HELTIONSHIP NOT ESTABLISHED. General weight loss, database to toles; Gastrointestinal; pancreatitis, hepatoma, colitis; Central Nervous System: confusion, convulsions, syncope; Eye: retinal edema; Genitourinary; decreased male fertility. Clinical Laboratory: positive antinuclear antibody; Hematopoietic: thrombocytopenia; Immunologic: anaphylaxis, Lupus-like syndrome, vasculitis; Integumentary: alopecia.

DOSAGE AND ADMINISTRATION. The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal MANAGEMENT OF OVERDOSE. While there has been no reported case of over-MANAGEMENT OF OVERDOSE. While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

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tion trial with gemfibrozil in middle-aged men with dyslipidemia. N Engl J Med
1987;317:1237-1245: 2. Manninen V, Elo O, Frick MH, et al: Lipid alterations and declin
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260:641-651. 3. Nikkila EA: Familial lipoprotein lipase deficiency and related disorders

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Exercise Test Predictors of Ambulatory Silent Ischemia During Daily Life in Stable Angina Pectoris

Prakash C. Deedwania and Enrique V. Carbajal, with the technical assistance of Kippur Sears

Which exercise test parameters have the highest predictive value for identifying patients at risk for silent ischemia in day-to-day life? Using simple mathematic formulas, we found early onset of ischemia, peak heart rate and peak systolic blood pressure during exercise testing to be the most significant parameters for patients with coronary artery disease and angina pectoris.

1157

Effects of Theophylline, Atenolol and Their Combination on Myocardial Ischemia in Stable Angina Pectoris

Filippo Crea, Giuseppe Pupita, Alfredo R. Galassi, Hassan El-Tamimi, Juan Carlos Kaski, Graham J. Davies, and Attilio Maseri

We studied the effects of theophylline, atenolol and their combination on myocardial ischemia in 9 patients with stable angina pectoris in a randomized, single-blind, triple crossover trial. Long-term administration of theophylline improves myocardial ischemia, but to a lesser degree than atenolol. The combination of theophylline and atenolol did not show detectable additive effects.

1163

Transient Left Ventricular Cavitary Dilation During Dipyridamole-Thallium Imaging as an Indicator of Severe Coronary Artery Disease

Jean Lette, Jacques Lapointe, David Waters, Michel Cerino, Michel Picard, and André Gagnon

Transient left ventricular cavitary dilation was seen in 45 of 510 consecutive patients referred for dipyridamole-thallium imaging. This study shows that transient LV dilation during dipyridamole-thallium imaging is a marker of severe underlying coronary artery disease and denotes a poor prognosis.

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Effects of Two Types of Fish Oil Supplements on Serum Lipids and Plasma Phospholipid Fatty Acids in Coronary Artery Disease

Gregg J. Reis, David I. Silverman, Theresa M. Boucher, Mary Ellen Sipperly, Gary L. Horowitz, Frank M. Sacks, and Richard C. Pasternak

In a placebo-controlled study, we examined the effects of 6 months of fish oil administration in 89 patients with coronary artery disease. Our results indicate that fish oil administration in patients with coronary artery disease is associated with potentially adverse changes in serum lipids.

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Predictive Value of Lipoprotein (a) and Other Serum Lipoproteins in the Angiographic Diagnosis of Coronary Artery Disease

James A. Hearn, Samuel J. DeMaio, Jr., Gary S. Roubin, Margareta Hammarstrom, and Demetrios Sgoutas

To assess the value of serum lipoproteins in predicting coronary artery disease, we assayed lipoproteins in 213 patients undergoing diagnostic angiography and assayed lipoprotein (a) in a subset of 98 CAD patients. When parameters including Lp(a) were analyzed by multivariate comparison, Lp(a) and the ratio of high-density lipoprotein to total cholesterol proved to be the best predictors of CAD.

1181

Voltage Criteria of Left Ventricular Hypertrophy in Sudden and Nonsudden Coronary Artery Disease Mortality: The Italian Section of the Seven Countries Study

Mariapaola Lanti, Paolo Emilio Puddu, and Alessandro Menotti

Of 1,588 persons without demonstrable coronary artery disease, 67 died suddenly and 87 died a nonsudden CAD death during the subsequent 20 to 23 years of follow-up. When a set of entry characteristics were analyzed, the 12-lead QRS voltage sum retained significant and independent relation to sudden death, whereas the Sokolow-Lyon index and ST-T alterations were associated with nonsudden CAD death.

1186

Videodensitometry Versus Digital Calipers for Quantitative Coronary Angiography

Hendrik du T. Theron, Charles R. Lambert, and Carl J. Pepine

We performed a prospective comparison of handheld digital caliper and computer-assisted videodensitometric analyses of coronary angiograms. We observed excellent correlations between area and diameter determinations between both methods, and more variability between caliper and videodensitometric area measurements in larger vessels. Intra- and interobserver variability was low for both methods.

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Frequency of Myocardial Indium-111 Antimyosin Uptake After Uncomplicated Coronary Artery Bypass Grafting

Bob van Vlies, Eric A. van Royen, Cees A. Visser, Nico G. Meyne, Monique M. G. van Buul, Ron J. G. Peters, and Arend J. Dunning

In 19 (82%) of 23 consecutive patients in whom indium-111 antimyosin scintigraphy specific for myocardial necrosis was performed after coronary artery bypass grafting, myocardial uptake was present, indicative of some degree of damage. Though no relation was found among uptake and ST-T

changes, isoenzyme levels, and duration of aortic cross-clamping and cardiopulmonary bypass, it is apparent that myocardial damage, though silent, is common after uncomplicated bypass grafting.

Usefulness of High-Frequency Analysis of Signal-Averaged Surface Electrocardiograms in Acute **Myocardial Infarction Before and After Coronary** Thrombolysis for Assessing Coronary Reperfusion

Bernardino Tranchesi, Jr., Marc Verstraete, Frans Van de Werf, Cicero P. de Albuquerque, Bruno Caramelli, Otavio C. Gebara, Wagner I. Pereira, Paulo Moffa, Giovanni Bellotti, and Fulvio Pileggi

We studied the incidence of late potentials before and after coronary thrombolysis in 54 patients with acute myocardial infarction. Coronary reperfusion reduces the incidence of late potentials and improves electrical stability of the heart; sensitivity and specificity of this finding are not high enough for reliable bedside monitoring of coronary reperfusion.

1199

Time Course and Prognostic Significance of Serial Signal-Averaged Electrocardiograms After a First **Acute Myocardial Infarction**

Luz M. Rodriguez, Ruud Krijne, Adri van den Dool, Pedro Brugada, Joep Smeets, and Hein J.J. Wellens

We prospectively assessed serial signal-averaged electrocardiograms recorded during 1 of the first 3 days, the second week and 6 months after a first myocardial infarction. Left ventricular ejection fraction is the strongest predictor of sustained ventricular tachycardia and ventricular fibrillation followed by duration of QRS complex recorded on 1 of the first 3 days of acute myocardial infarction. Sudden death was only predicted by left ventricular ejection fraction.

1203

Prognostic Value of Predischarge Low-Level Exercise Thallium Testing After Thrombolytic Treatment of **Acute Myocardial Infarction**

Peter L. Tilkemeier, Timothy E. Guiney, Paul J. LaRaia, and Charles A. Boucher

We evaluated 67 patients after acute reperfusion therapy for acute myocardial infarction and 107 patients without acute intervention, using predischarge low-level thallium testing, and followed them for a mean of 367 days for repeat cardiac events. Tests presumed to be useful after an AMI may not have similar prognostic usefulness after acute intervention after an AMI.

Prognosis of Acute Myocardial Infarction Complicated by Primary Ventricular Fibrillation

Solomon Behar, Uri Goldbourt, Henrietta Reicher-Reiss, Elieser Kaplinsky, and the Principal Investigators of the **SPRINT Study**

The incidence of primary ventricular fibrillation in 5,839 consecutive patients with acute myocardial infarction was 2.1%. In-hospital mortality rate was 18.8% in 122 patients with primary VF compared with 8.5% in 3,707 patients forming the reference group. Primary VF exerts an independent, significant effect on in-hospital mortality.

ARRHYTHMIAS AND CONDUCTION DISTURBANCES

Usefulness of Labetalol in Chronic Atrial Fibrillation

Cheuk-Kit Wong, Chu-Pak Lau, Wing-Hung Leung, and Chun-Ho Cheng

To see if labetalol—a β blocker with α -blocking properties would control heart rate without decreasing exercise tolerance in patients with chronic atrial fibrillation without underlying structural heart disease, we studied 10 patients in a 4-phase, double-blind exercise and electrocardiographic comparison of labetalol, in full dose or as an adjunct to digoxin, placebo and digoxin monotherapy.

1216

Usefulness of Combined Propranolol and Verapamil for Evaluation of Surgical Ablation of Accessory Atrioventricular Connections in Patients Without Structural Heart Disease

Simón Milstein, Ann Dunnigan, Jeffrey Buetikofer, David G. Benditt, Jane Crosson, and Edgar Pineda

In 17 patients undergoing surgical ablation of accessory connection, we gave combined intravenous propranolol and verapamil pre- and postoperatively. Our results indicate that the combined administration of propranolol and verapamil may prove helpful for differentiating between retrograde atrioventricular nodal and residual accessory connection conduction during early postoperative assessment of patients undergoing surgery for accessory AV connection ablation.

1222

Long-Term Effect of Mexiletine on Left Ventricular Function and Relation to Suppression of Ventricular **Arrhythmia**

Steven Singh, Richard Klein, Brian Eisenberg, Edward Hughes, Margaret Shand, and Pat Doherty, with the technical assistance of Gerhard Sharon

The effects of oral mexiletine on left ventricular ejection fraction and ventricular arrhythmias were evaluated during 3 months of therapy in 29 patients with ventricular premature complexes and a moderately reduced LVEF. Long-term use of mexiletine is efficacious and relatively free of cardiac depressant effects even in patients with diminished LV function.

SYSTEMIC HYPERTENSION

1228

Effectiveness of the Once-Daily Calcium Antagonist, Lacidipine, in Controlling 24-Hour Ambulatory Blood

Mary E. Heber, Paul A. Broadhurst, Geoffrey S. Brigden, and Edward B. Raftery

The efficacy of the new once-daily dihydropyridine calcium antagonist lacidipine in reducing ambulatory intraarterial blood pressure was assessed in 12 untreated hypertensive patients. Blood pressure was reduced throughout the 24-hour period, there was no postural hypotension, and there was successful attenuation of the pressor response to isometric and dynamic exercise.

CONGENITAL HEART DISEASE

1233

Atenolol Therapy for Exercise-Induced Hypertension After Aortic Coarctation Repair

Rae-Ellen W. Kavey, John L. Cotton, and Marie S. Blackman

There is a high incidence of premature cardiovascular disease after coarctation repair even when surgery has eliminated resting arm/leg gradients. Exercise-induced upper body systolic hypertension, a well-documented postoperative finding, may contribute to the etiology of this. In 9 of 10 children reported here, treatment with cardioselective β blockade eliminated the hypertensive upper body response to exercise. In theory, this should reduce the risk of premature coronary artery disease.

MISCELLANEOUS

1237

Risk of Cardiovascular Mortality in Alcohol Drinkers, **Ex-Drinkers and Nondrinkers**

Arthur L. Klatsky, Mary Anne Armstrong, and Gary D. Friedman

The results of this study of 1,002 cardiovascular deaths among 123,840 persons indirectly support the thesis that lighter amounts of alcohol have a protective effect against coronary artery disease. Although the risk of death from all causes was highest among those who drank large amounts of alcohol, persons who usually take up to 1 to 2 drinks per day should not be advised to abstain from alcohol in order to reduce their risk of cardiovascular death.

Subnormal Parasympathetic Activity After Cardiac Transplantation

Michael L. Smith, Kenneth A. Ellenbogen, Dwain L. Eckberg, Helen M. Sheehan, and Marc D. Thames

Heart period variability was measured in 18 patients with congestive heart failure before and after cardiac transplantation and in 16 age-matched control subjects. In the denervated donor atria, this variability did not change from early to late posttransplantation, suggesting that vagal reinnervation of the donor heart had not occurred. Data indicate that baseline parasympathetic activity does not increase significantly during the first month after transplantation but increases significantly between months 3 and 6.

Natural History of Cardiac Rhabdomyoma in Infancy and Childhood

John F. Smythe, John D. Dyck, Jeffrey F. Smallhorn, and Robert M. Freedom

We reviewed our experience with rhabdomyoma in infancy over a 20-year period. Results suggest that pediatric cardiac rhabdomyoma is most often a benign condition in which spontaneous regression is the rule. Surgery is recommended only for patients with refractory dysrhythmias or severe hemodynamic compromise.

EDITORIAL

Is the Term "Tricuspid Atresia" Appropriate?

P. Syamasundar Rao

BRIEF REPORTS

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Supported Coronary Angioplasty and Standby Supported Coronary Angioplasty for High-Risk **Coronary Artery Disease**

Carl L. Tommaso, Rodney A. Johnson, J. Lawrence Stafford, Albert R. Zoda, and Robert A. Vogel

Prognosis of Congestive Heart Failure in Elderly Patients with Normal Versus Abnormal Left Ventricular Systolic Function Associated with Coronary Artery Disease

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Natural History of Posterobasal Left Ventricular Aneurysm

Morteza Amidi, Steven Royal, Edward Curtiss, and Maureen Puskar

Physician Attitudes Toward the Use of Type IC Antiarrhythmics After the Cardiac Arrhythmia **Suppression Trial (CAST)**

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Treatment of Ventricular Arrhythmias in Children Without Structural Heart Disease With Class IC Agents as Guided by Invasive Electrophysiology

Christopher L. Case and Paul C. Gillette

Safety and Efficacy of In-Office Cardioversion for **Treatment of Supraventricular Arrhythmias**

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Effects of Amlodipine on Blood Pressure, Heart Rate, Catecholamines, Lipids and Responses to Adrenergic

Larry M. Lopez, Alfred D. Thorman, and Jawahar L. Mehta

1277 1271 Frequencies of Reactions to Iohexol Versus loxaglate Effect of Mitral Regurgitation on the Left Ventricular James L. Vacek, Lisa Gersema, Mark Woods, Carol Bower, **Outflow Pressure Gradient in Obstructive Hypertrophic** and Gary D. Beauchamp Cardiomyopathy Paul A. Tunick, Rachel Lampert, John L. Perez, and Itzhak Kronzon Safety and Usefulness of Transesophageal Echocardiography in Persons Aged ≥70 Years Elizabeth O. Ofili and Michael W. Rich, with the technical **Combined Obstructive Hypertrophic Cardiomyopathy** assistance of Peggy Brown and Jean Lewis and Stenotic Congenitally Bicuspid Aortic Valve Paul S. Brown, Jr., Charles Stewart Roberts, Charles L. McIntosh, William C. Roberts, and Richard E. Clark

Experience with the Gianturco-Roehm Bird's Nest

Bryan Martin, Thomas E. Martyak, Thomas L. Stoughton,

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Vena Cava Filter

William A. Collazo, and William Pearl

BALANCED CARDIODYNAMICS... THE LINK TO ANTIANGINAL PROTECTION AND SAFETY

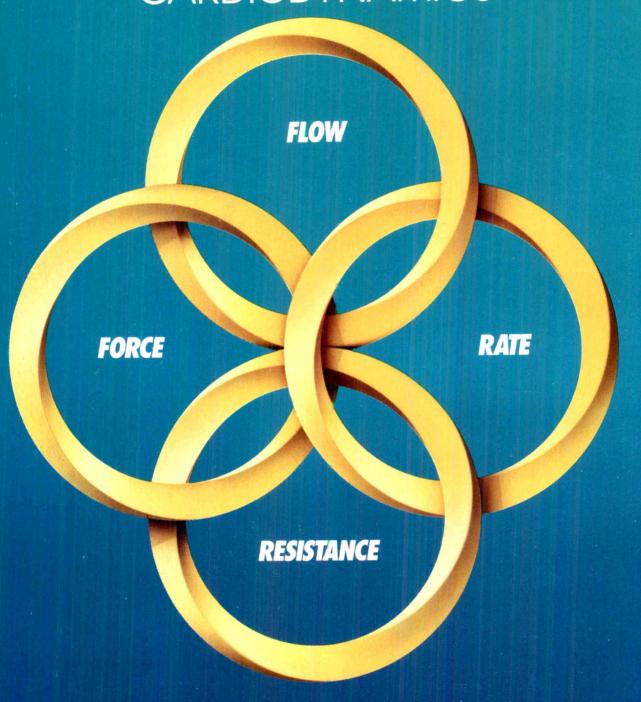


CARDIZE

diltiazem HCI TABLETS
90 mg tid

CARDIZEM: ANTIANGINAL

BALANCED CARDIODYNAMICS



* CARDIZEM (diltiazem HCI) is indicated in the treatment of angina pectoris due to coronary artery spasm and in the management of chronic stable angina (classic effort-associated angina) in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents.

t Caution should be used in nations with CHF

PROTECTION AND SAFETY



Cardizem increases coronary blood flow 1-4,8-11

—giving patients more pain-free days 10-12*



Cardizem often achieves desirable reductions in heart rate 13,842

-without slowing patients down



Cardizem decreases peripheral resistance and myocardial work load 1-4

—so patients can do more



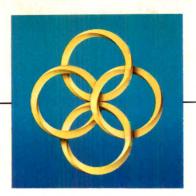
Cardizem has little or no effect on myocardial contractile force

 with virtually no clinically significant negative inotropic effect in patients with normal LV function 1-3,5-8

BALANCED CARDIODYNAMICS ARE WHAT MAKE CARDIZEM

CARDIZEM Adiltiazem HCI TABLETS 90 mg tid

Please see brief summary of prescribing information on next page.



diltiazem HCl

MAKING THE DIFFERENCE IN ANGINA







60 ma

90 mg

120 mg

BRIEF SUMMARY

CARDIZEM*
(diltiazem HCI) Tablets

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular poce-maker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by x-ray an admission.

WARNINGS

Cardiac Conduction. CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect time, except in patients with sick sinus syndrome. This element may rarely result in obnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1, 243 patients for 0, 48%). Concomitant use ditiliazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's and statements are considered to the patient with Prinzmetal's and statements. gina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.

Congestive Heart Failure. Although diltiazem has a negative

congestive near ratifier. All most respective preparations, hemody-namic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in po-tients with impaired ventricular function is very limited. Caution

should be exercised when using the drug in such patients.

Hypotension. Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic

hypotension.

Acute Hepatic Injury. In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in most cases, but prabable in some. (See PRECAUTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subocute and chronic dog and rat studies designed to produce toxicity, high doses of diffiazem were associated with hepatic dam-age. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema mul-tiforme and/or extalliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any agents known to affect cardiac contractility and/or conduction. (See WARNINGS.)

and/or conduction. Gee windings.)

Pharmacologic-studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytechrome P-450 mixed function oxidose. Coadministration of CARDIZEM with other agents which follow the

inhibition of metabolism. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting r stopping concomitantly administered CARDIZEM to maintain aptimum therapeutic blood levels.

optimum merapeuric blood levels.

Beta-blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of CARDIZEM (diltiazem hydrochloride) concom itantly with propranolol in five normal valunteers resulted in in-creased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50% if combination therapy is initiated or withdrawn inconjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine: A study in six healthy volunteers has shown a Cimertaine: A study in six receimly volunteers had snown a significant increase in peak dilitiozem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimertaine at 1.200 mg per day and dilitiozem 60 mg per day Ranifidine produced smaller, nonsignificant increases. The effect may be mediated by cimertidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis: Administration of CARDIZEM with digoxin in 24

healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid

possible over- or under-digitalization. (See WARNINGS.)

Anesthetics: The depression of cardiac cantractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed

Pregnancy, Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

Cardizemo

Usual maintenance dosage 180 to 360 mg/day

There are no well-controlled studies in pregnant women; there-fore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alterna-

tive method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded

Deen excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacol-

which can be diffest reasonably associated with the printion-ogy of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occur-rences as well as their frequency of presentation are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), astheria (1.2%), in addition, the following events

rosn (1.3%), Staterial (1.2%). In dualinar, in a billowing even is were reported infrequently (less than 1%):

Cardiovascular: Angina, arrhythmia, AV block (first degree), AV block (second or third degree — see conduction warning), bradycardia, congestive heart failure, flushing, hypotension, palpitations,

syncope.

Nervous System: Arnnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor

tremor.

Arorexia, constipation, diarrhea, dysgeusia, dyspepsia, mild elevations of alkaline phospholose, SGOT, SGPT, and LDH (see hepatic warnings), vomiting, weight increase.

Petechiae, prartius, photosensitivity, urticaria.

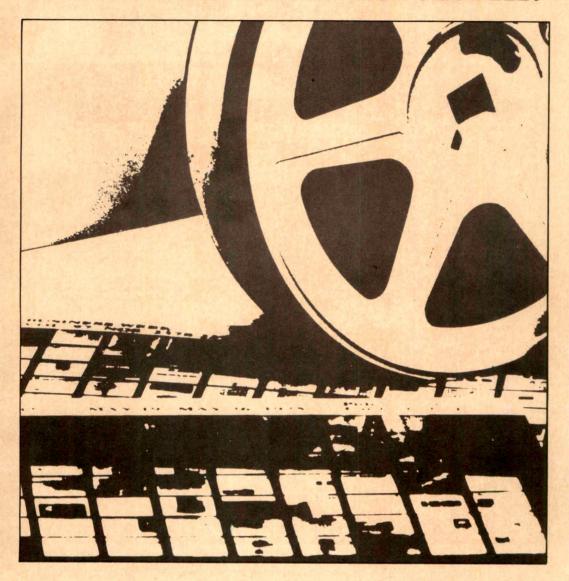
Dermatologic: Amblyapia, CPK elevation, dyspnea, epistaxis.

eye irritation, hyperglycemia, nasal congestion, nacturia, osteoarticular pain, polyuria, sexua difficulties.

The following postmorketing events have been reported infre-quently in patients receiving CARDIZEM: alopecia, gingival hyperplasia, erythema multiforme, and leukopenia. How er, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established

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American Journal of Cardiology

NOVEMBER 15, 1990, VOL. 66, NO. 17

CORONARY ARTERY DISEASE

1151

Exercise Test Predictors of Ambulatory Silent Ischemia During Daily Life in Stable Angina Pectoris

Prakash C. Deedwania and Enrique V. Carbajal, with the technical assistance of Kippur Spears

Several exercise test parameters were examined for their ability to predict risk of ambulatory silent ischemia. Of 86 patients with coronary artery disease, stable angina and a positive exercise test, 39 (45%, group 1) had ≥1 episodes of transient ischemia and 47 (group 2) did not develop ST changes during ambulatory electrocardiographic monitoring. Comparison of exercise parameters revealed significant differences between patients with and without ambulatory silent ischemia. Although the peak heart rate (p <0.05) and peak systolic blood pressure (p <0.01) were significantly lower in the group 1 patients, the onset of ischemia during exercise was found to be the most important (p < 0.0005) predictor. There was a significant (p < 0.005, r = -0.32) correlation between the earlier onset of exercise-induced ischemia and the duration of ambulatory silent ischemia. Simple mathematic formulas for calculating the risk of ambulatory silent ischemia are provided.

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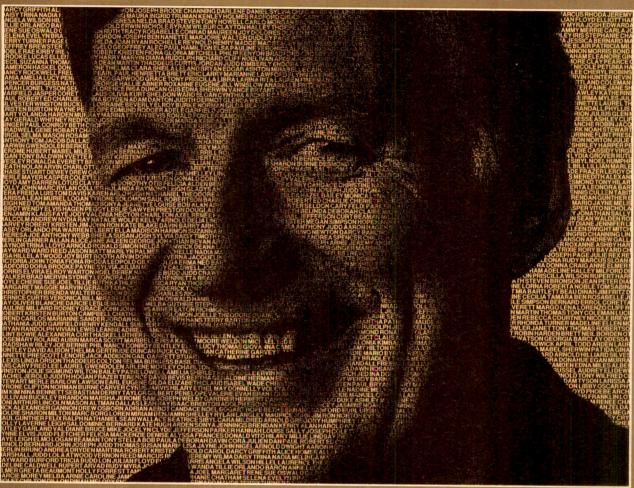
Effects of Theophylline, Atenolol and Their Combination on Myocardial Ischemia in Stable Angina Pectoris

Filippo Crea, Giuseppe Pupita, Alfredo R. Galassi, Hassan El-Tamimi, Juan Carlos Kaski, Graham J. Davies, and Attilio Maseri

The effects of theophylline (400 mg twice a day), atenolol (50 mg twice a day) and their combination on myocardial ischemia were studied in 9 patients with stable angina pectoris in a randomized, single-blind, triple crossover trial. Placebo was administered to patients during the run-in and the run-off periods. A treadmill exercise test and 24-hour ambulatory electrocardiographic monitoring were obtained at the end of each treatment period. Theophylline, compared with placebo, significantly improved the time to onset of myocardial ischemia and the exercise duration. During atenolol and during combination treatment the time to onset of ischemia and the exercise duration were similar and significantly longer than during theophylline administration. During ambulatory electrocardiographic monitoring theophylline, compared with placebo, significantly decreased the total ischemic time. During combination treatment the total ischemic time was not different from that during atenolol, although it was

Continued on page A18

EXPECT YOUR NEXT PATIENT TO Feel like M I L L O N



... like the more than one million patients who have received INDERAL LA for hypertension, angina, and common-migraine prophylaxis.



LONG ACTING CAPSULES 60,80,120,160 mg



INDERAL LA should not be used in the presence of congestive heart failure, sinus bradycardia, cardiogenic shock heart block greater than first degree, and bronchial asthma.

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)

INDERAL® LA brand of propranolol hydrochloride (Long Acting Capsules)

DESCRIPTION. INDERAL LA is formulated to provide a sustained release of propranolol hydrochloride. INDERAL LA is available as 60 mg, 80 mg, 120 mg, and 160 mg capsules.

CLINICAL PHARMACOLOGY. INDERAL is a nonselective, beta-adrenergic receptor-blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor-stimulating agents for available receptor sites when access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vaso-dilator responses to beta-adrenergic stimulation are decreased proportionately. INDERAL LA Capsules (60, 80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours. When measured at steady state over 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL Tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially.

hour period, blood levels are fairly considered a simple mg-for-mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure, and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period.

INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension; it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the

Angina Pectoris Due to Coronary Atherosclerosis: INDEHAL LA is indicated for the long-term management of patients with angina pectoris.

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headabe. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary.

is contraindicated in 1) cardiogenic shock; 2) sinus CONTRAINDICATIONS. INDERAL

ONCE-DAILY

LONG ACTING CAPSULES

NDERAL LA

bradycardia and greater than first-degree block; 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with

WARNINGS, CARDIAC FAILURE: Sympa warnings, CARIDIAC FAILURE: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving clinitalis and

compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on

heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually. if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and in some cases, myocardial infarction, following abruar discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned, the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosciencies heart disease who are given progranded for other indications. atherosclerotic heart disease who are given propranolol for other indications

atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (eg, chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors. MAJOR SURGERY The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL (propranolol HCI), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, eg, dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotlension. DIRECTIVE in starting and maintaining the heartbeat has also been reported with beta blockers. DIABETES AND HYPOGLYCEMIA: Beta blockers should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. Following insulin-induced hypoglycemia, propranolol may cause a delay in the recovery of blood glucose to normal levels.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism, including thyroid storm. Propranolol may change thyroid function tests, increasing 14 and reverse 15, and decreasing 13. IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case, this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS. GENERAL: Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL (propranolol HCI) is not indicated for the treatment of hypertensive emergencies.

Beta-adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be lold that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a

Beta-adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be lold that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

CLINICAL LABORATORY TESTS: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase. DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL (propranolol HC) is administered. The addicateholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension. marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Caution should be exercised when patients receiving a beta blocker are administered a calcium-channel-blocking drug, especially intravenous verapamil, for both agents may depress myocardial contractility or atrioventricular conduction. On rare occasions, the concomitant intravenous use of a beta blocker and verapamil has resulted in serious adverse reactions, especially in patients with severe cardiomyopathy, congestive heart failure, or recent myocardial infarction.

Aluminum hydroxide gel greatly reduces intestinal absorption of propranolol. Ethanol slows the rate of absorption of propranolol. Phenytoin, phenobarbitone, and rifampin accelerate propranolol clearance. Chlorpromazine, when used concomitantly with propranolol. results in increased plasma levels of both drugs.

Antipyrine and lidocaine have reduced clearance when used concomitantly with propranolol.

Thyroxine may result in a lower than expected T₃ concentration when used concomitantly with propranolol.

hyroxine may result in a lower than expected T₃ concentration when used concomitantly

with propranolol Cimetidine decreases the hepatic metabolism of propranolol, delaying elimination and

Cimetidine decreases the hepatic metabolism of propranolol, delaying elimination and increasing blood levels.

Theophylline clearance is reduced when used concomitantly with propranolol. CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18 month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment fertility that was attributable to the drug.

PREGNANCY: Pregnancy Category. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. NURSING MOTHERS: INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

PEDIATRIC USE: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely

ADVERSE REACTIONS. Most adverse effects have been mild and transletted by required the withdrawal of therapy.

Cardiovascular: Bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; thrombocytopenic purpura; arterial insufficiency, usually of the Raynaud type.

Central Nervous System: Light-headedness; mental depression progressing to catatonia; visual disturbances; hallucinations; vivid dreams; are acute reversible syndrome characterized by discrientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics. For immediate formulations, fatigue, lethargy, and vivid

mance on neuropsychometrics. For immediate formulations, fatigue, lethargy, and vivit dreams appear dose related. Gastrointestinal. Nausea, vomiting, epigas tric distress, abdominal cramping, diarrhea constipation, mesenteric arterial thrombosis ischemic colitis.

Allergic: Pharyngitis and agranulocytosis erythematous rash, fever combined with aching and sore throat, laryngospasm and respira tory distress.

Respiratory: Bronchospasm

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura. Auto-Immune: In extremely rare instances, systemic lupus erythematosus has bee reported

Miscellaneous: Alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence and Peyronie's disease have been reported rarely Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolal) have no been associated with propranolol

DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in sustained-release capsule for administration once daily. If patients are switched from INDERAL Tablets to INDERAL LA Capsules, care should be taken to assure that the desired therapeuti effect is maintained. INDERAL LA should not be considered a simple mg-for-mg substitute for INDERAL INDERAL LA has different kinetics and produces lower blood levels. Retitration mabe necessary, especially to maintain effectiveness at the end of the 24-hour dosing interval. HYPERTENSION — Dosage must be individualized. The usual initial dosage is 80 m INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may b increased to 120 mg once daily or higher until adequate blood-pressure control is achiever. The usual maintenance dosage is 120 to 160 mg once daily. In some instances a dosage of 64 mg may be required. The time needed for full hypertensive response to a given dosage ivariable and may range from a few days to several weeks.

ANGINA PECCORIS.—Operage must he individualized. Starting with 80 mg INDERAL INDERAL.

mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

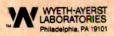
ANGINA PECTORIS—Dosage must be individualized. Starting with 80 mg INDERAL Lonce daily, dosage should be gradually increased at three- to seven-day intervals until optimit response is obtained. Although individual patients may respond at any dosage level, the average optimal dosage appears to be 160 mg once daily. In angina pectoris, the value an safety of dosage exceeding 320 mg per day have not been established. If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (se WARNINGS).

WAHNINGS).

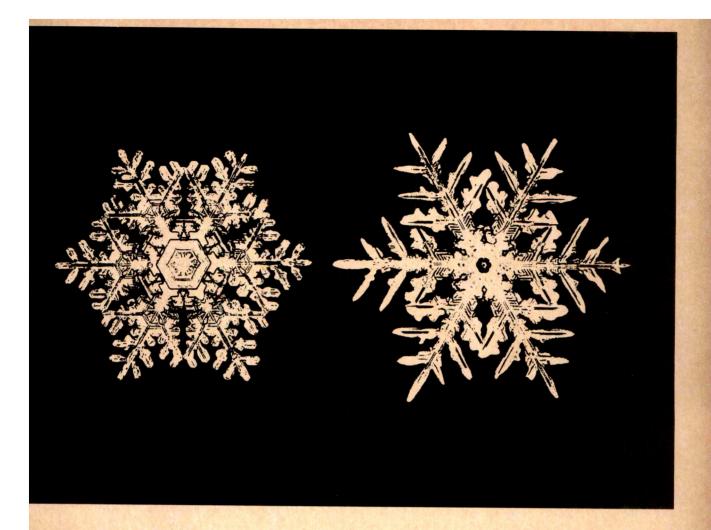
MIGRAINE — Dosage must be individualized. The initial oral dose is 80 mg INDERAL L once daily. The usual effective dose range is 160-240 mg once daily. The dosage may be increased gradually to achieve optimal migraine prophylaxis. If a satisfactory response is notained within four to six weeks after reaching the maximal dose, INDERAL LA therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of sever wankley.

weeks.
HYPETROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily.
PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are to limited to permit adequate directions for use.

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Because body chemistry differs from person to person, we often need a choice of drugs to treat the same illness.

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significantly lower than that observed during theophylline. Thus, in patients with stable angina pectoris long-term oral administration of theophylline improved myocardial ischemia, but to a lesser degree than atenolol. The combination of theophylline and atenolol did not show detectable additive effects.

1163

Transient Left Ventricular Cavitary Dilation During Dipyridamole-Thallium Imaging as an Indicator of Severe **Coronary Artery Disease**

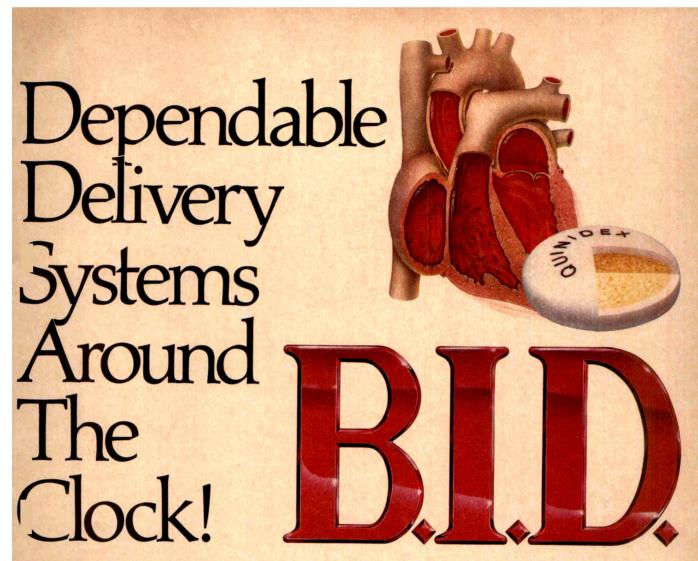
Jean Lette, Jacques Lapointe, David Waters, Michel Cerino, Michel Picard, and André Gagnon

Transient left ventricular (LV) cavitary dilation was observed in 45 (9%) of 510 consecutive patients referred for dipyridamole-thallium imaging. Coronary angiography was performed in 32 patients: 75% had either left main, 3-vessel or "high-risk" 2-vessel coronary artery disease. Although 25 of 45 patients (56%) were either asymptomatic or had grade 1/4 effort angina, 16 of 25 (64%) with transient cavitary dilation who did not undergo coronary revascularization sustained a cardiac event (nonfatal myocardial infarction or cardiac death) after a mean follow-up of 12 months. There was a 58% postoperative cardiac event rate in 12 patients with reversible cavitary dilation who underwent noncardiac surgery. Transient LV dilation during dipyridamole-thallium imaging is a marker of severe underlying coronary artery disease and denotes a poor prognosis.

Effects of Two Types of Fish Oil Supplements on Serum Lipids and Plasma Phospholipid Fatty Acids in Coronary Artery

Gregg J. Reis, David I. Silverman, Theresa M. Boucher, Mary Ellen Sipperly, Gary L. Horowitz, Frank M. Sacks, and Richard C. Pasternak

The effects of fish oil supplementation on serum lipids remain controversial. This placebo-controlled study examined the effects of 6 months of fish oil administration in 89 patients with coronary artery disease. Subjects were randomly assigned to receive 12 capsules/day containing 1 of 2 types of fish oil, or olive oil. Triglyceride levels decreased by 28 to 32%, and lowdensity lipoprotein (LDL) cholesterol levels increased by 3 to 12% in the fish oil groups. The changes were most pronounced in hypertriglyceridemic subjects, in whom LDL cholesterol increased by 14 to 23%. Plasma levels of eicosapentaenoic acid increased by fivefold in the fish oil groups. The increase in LDL cholesterol was weakly correlated with achieved eicosapentaenoic acid level. Fish oil administration in patients with coronary artery disease is associated with potentially adverse changes in serum lipids.



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*Some patients may require t.i.d. dosing.



(Quinidine Sulfate Extendedrelease Tablets, USP) 300 mg

A-H-ROBINS

Pharmaceutical Division, Richmond, Virginia 23261-6609 ©A. H. Robins Company 1987

Please see adjacent page for brief summary.

EXTENTABS

(Quinidine Sulfate Extendedrelease Tablets, USP) 300 mg

The following is a brief summary only. Before prescribing, see complete prescribing information in Quinidex product labeling.

information in Quinidex product labeling.

Contraindications: Intraventicular conduction defects. Complete A-V block. A-V conduction disorders caused by digitals intoxication. Aberrant impulses and abnormal rhythms due to escape mechanisms. Idiosyncrasy or hypersensitivity to quinidine or related cinchose deriradiuse. Mysterina gravis.

Warnings: in the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 11 ratio, resulting in an externelly rapid ventricular rate. This possible hazard may be reduced by digitalization prior to administration of quinidine. Reports in the literature indicate that serum concentrations of digitals involving. Reduction of digitals would, Reduction of digitals would, Reduction of digitals would, Reduction of digitals with a digital consisting of the DRS complex and ventricular tachyarthythmias mandate immediate discontinuation of the drug and/or close clinical and electrocardiographic monitoring.

interval, widening of the Un's Confugie and retentional and electrocardiographic monitoring. In susceptible individuals, such as those with marginally compensated cardiovascular disease, quindine may produce clinically important depression of cardiac function manifested by hypotension backgradia, or heartiflicts. Quindine therapy should be carefully monitored in such individuals. Quindine should be used with externe caution in patients with incomplete AV block since complete AV block and asystole may be produced. Quindine may cause abnormalities of cardiac hythrin digitalized patients and therefore should be used with caution in the presence of dipitalis intoxication. Quindine should be used with caution in patients exhibiting renal, cardiac or hepatic insufficiency because of potential accumulation of quindine in serum, leading to toxicity. Patients taking quindine occasionally have synocoal episodes which usually result from ventricular tachvardia or fibrillation. This syndrom has not been shown to be related to dose or serum levels. Synocoal episodes frequently terminate spontaneously or in response to treatment, but sometimes are table. Cases of hepatoloxicity, including granulomatous hepatitis, due to quindine in hyperessistivity have been reported. Unexplained lever and/or elevation of hepatic enzymes, particularly in the early stage of therapy, warrant consideration of possible hepatoloxicity. Monitoring liver function during the first 4-8 weeks should be considered. Cessation of quindine in mese cases usually results in the disappearance of loxicity. Precautions: General—Alt the precautions applying to regular quindine therapy apply to this product. Hypersensitivity or anaphysticid tractions to quindine, although rare, should be considered, especially during the firsts weeks of therapy, visipalization for close clinical observation, electrocardiographe monitoring, and determination of serum quindine levels are indicated when large doses of quindine are used or with patients who present an increased risk

tor close clinical object valuation, electrocharge process of quindine are used or with patients who present an increased risk. Information for Patients—As with all solid dosage medications, Quinidex Extentats should be taken with an adequate amount of fluid, preferably with the patient in an unpright position to lacilitate swallowing. They should be swallowed whole in order to preserve the controlled-release mechanism.

Laboratory Tests—Periodic blood counts and liver and kidney function tests should be performed during long-term therapy; the drug should be discontinued if blood dyscrasias or evidence of hepatic or renal dystunction occurs.

Drug Interactions

Drug

Quindine with anticholinergic drugs
Quindine with anticholinergic drugs
Quindine with carbonic antity-drase inhibitors, sodium bicarbonate, thisaide directes countries and continued in decreased exception of quindine effects of quindine with courserin anticoagulates

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anticoagulants
Quinidine with tubocurare

antisses,
Quindine with tubocurare
succipycholine and
decamethonium
Quindine with phenothizines
and reserpine
and reserpine
Avaindine with hepatic enzymeAvaindine with hepatic enzymeand reserpine

Quinidine with hepatic enzymeinducing drugs (phenobarbital,
phenytoin, rifampin)

Quinidine with digoxin

phenytoin, rifampin)
Quinidine with digoxin

Quinidine with amiodarone
Quinidine with cimetidine
Quinidine with rantitidine
Quinidine with rantitidine
Quinidine with verapamil

Quinidine with verapamil

Quinidine with verapamil

Quinidine with rifedipine
Carcinogenesis: Studies in animals have not been performed to evaluate the carcinogency of the carcinogenesis with the carcinogenesis animals have not been performed to evaluate the carcinogenic potential of Quinidine.

Caranogenesis: Studies in aliminals have in users a few more in each compension of quindine.

Prepnancy. Teratogenic Effects: Prepnancy Category C. Animal reproduction studies have not been conducted with quindine. There are no adequate and well-controlled studies in pregnant women. Quindex Extentabs should be administered to a pregnant woman only if clearly indicated.

Monteratogenic Effects: Like quinine, quindine has been reported to have oxytocic properties. The significance of this property in the clinical setting has not been

Monteratogenic Effects: Like quinine, quinidine has been reported to have oxylocic properties. The significance of this property in the clinical setting has not been established.

Labor and Delivery—There is no known use for Quinidex Estenials in labor and delivery However, quinidine has been reported to have oxylocic properties. The delivery However, quinidine has been reported to have oxylocic properties. The delivery However, quinidine has been reported to have oxylocic properties. The delivery However of this property in the clinical setting has not been established.

Mursing Mothers—Becase of passage of the drug into breast milk, caution should be exercised when Quinious Koteniabs are administered to a nursing woman.

Pediatric Use—There are no adequate and well-controlled studies establishing the safety and effectiveness of Quinious Circhonisms, such as ringing in the ears, loss of hearing, dizziness, lightheadedness, headache, nausea, and/or disturbed vision may appose in sensitive patients after a single dose of the drug. The most frequently encountered side effects to quinidine are pastrointestinal.

Gastrointestinal—Nauses, vomitting, abdominal pain, diarrhea, anorexia, granulomatous hepatitis (which may be preceded by fever), esophagitis.

Cardiovascular—Ventricular extrasystoles occurring at a rate of one or more every 6 normal beats; widening of the QRS complex and prolonged OT interva; complete A-V block, ventricular tachycardia and fibrillation; ventricular fulter; torsace de pointes; arterial embolism, hypotension, syrcope.

Central Nervous System—Headache, vertigo, apprehension, excitement, confusion, editrum, dementia, alaxia, depression.

Ophthalmologic and Otologic—Usilish Studied color perception, photophobia, diplopia, night blindness, scolornata, optic neurilis, educed vsual field.

Dermatologic—Vulenes us fushing with intense prurilus, photosensitivity—Angloedem—Autoropenia, brumachoropenia currinary, agamulocytosis.

Almatologic—Systemic lupus erythematosus, lupus nephritis.

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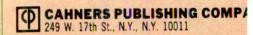
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Predictive Value of Lipoprotein (a) and Other Serum Lipoproteins in the Angiographic Diagnosis of Coronary Artery Disease

James A. Hearn, Samuel J. DeMaio, Jr., Gary S. Roubin, Margareta Hammarstrom, and Demetrios Sgoutas

Associations among age, gender, hypertension and other risk factors with coronary artery disease (CAD) were studied in 213 patients undergoing angiography with measurements made with the aid of digital calipers. All risk factors except gender, hypertension, diabetes mellitus and cigarette smoking were univariate predictors of CAD. Multivariate predictors for CAD were family history, age, high-density lipoprotein cholesterol, total cholesterol and apolipoprotein (apo) B. When lipoprotein (a) [Lp(a)] was included (in 98 patients of the 192 with CAD), multivariate predictors for CAD were age, family history, apo B and Lp(a). Lipid parameters alone showed the high-density lipoprotein/total cholesterol ratio and Lp(a) to be the best discriminators.

Voltage Criteria of Left Ventricular Hypertrophy in Sudden and **Nonsudden Coronary Artery Disease Mortality: The Italian Section of the Seven Countries Study**

Mariapaola Lanti, Paolo Emilio Puddu, and Alessandro Menotti

Of 1,588 persons free of demonstrable coronary artery disease (CAD) at entry examination in 1962, 67 died suddenly and 87 died a nonsudden CAD death during the subsequent 20 to 23 years of follow-up. When a set of entry characteristics were analyzed, including mean blood pressure and ST-T abnormalities, and 3 voltage criteria of left ventricular (LV) hypertrophy, the 12-lead QRS voltage sum retained significant and independent relation to sudden death (t = 2.00), whereas the Sokolow-Lyon index and ST-T alterations were associated with nonsudden CAD death (t = -2.10and t = 2.19, respectively). This investigation points to the usefulness of the electrocardiogram and to derived voltage criteria of LV hypertrophy for risk stratification in apparently healthy persons during long-term follow-up.

1186

Videodensitometry Versus Digital Calipers for Quantitative Coronary Angiography

Hendrik du T. Theron, Charles R. Lambert, and Carl J. Pepine

A prospective comparison of handheld digital caliper and computer-assisted videodensitometric (Vanguard XR-70) analyses of coronary angiograms was performed. Excellent correlations were observed between area and diameter determinations between both methods. More variability between caliper and videodensitometric area measurements was observed in larger vessels. Intra- and interobserver variability was low for both methods.

1191

Frequency of Myocardial Indium-111 Antimyosin Uptake After Uncomplicated Coronary Artery Bypass Grafting

Bob van Vlies, Eric A. van Royen, Cees A. Visser, Nico G. Meyne, Monique M. G. van Buul, Ron J. G. Peters, and Arend J. Dunning

Indium-111 antimyosin scintigraphy, specific for myocardial necrosis, was performed in 23 consecutive patients after uncomplicated coronary bypass grafting. Before surgery all patients had stable angina and no history of myocardial infarction. In 19 patients (82%), myocardial uptake of indium-111 antimyosin was present, indicative of some degree of myocardial damage. No relation was found among antimyosin uptake and electrocardiographic changes, isoenzyme levels and duration of both aortic cross-clamping and cardiopulmonary bypass. It is concluded that myocardial damage to some extent, though silent, is common after uncomplicated bypass grafting.

1196

Usefulness of High-Frequency Analysis of Signal-Averaged Surface Electrocardiograms in Acute Myocardial Infarction Before and After Coronary Thrombolysis for Assessing Coronary Reperfusion

Bernardino Tranchesi, Jr., Marc Verstraete, Frans Van de Werf, Cicero P. de Albuquerque, Bruno Caramelli, Otavio C. Gebara, Wagner I. Pereira, Paulo Moffa, Giovanni Bellotti, and Fulvio Pileggi

A significant 50% relative reduction in the incidence of late potentials on the signal-averaged electrocardiogram was observed in 35 patients with angiographically proven coronary reperfusion (from 16 of 35 before to 8 of 35 afterward). No significant reduction was seen in 19 patients in whom thrombolysis was unsuccessful. It is concluded that coronary reperfusion reduces the incidence of late potentials and thus improves the electrical stability of the heart but that the sensitivity and specificity of this finding are not high enough for reliable bedside monitoring of coronary reperfusion.

1199

Time Course and Prognostic Significance of Serial Signal-Averaged Electrocardiograms After a First Acute Myocardial Infarction

Luz M. Rodriguez, Ruud Krijne, Adri van den Dool, Pedro Brugada, Joep Smeets, and Hein J.J. Wellens

The prognostic significance of serial signal-averaged electrocardiograms recorded during the first 3 days (period 1), in the second week (period 2) after a first myocardial infarction and 6 months later (period 3) was prospectively assessed in 190 patients. Multivariate regression analysis using continuous variables showed that the strongest predictor of sustained ventricular tachycardia and ventricular fibrillation was left ventricular ejection fraction (p <0.0001) followed by the duration of the QRS complex on the signal-averaged electrocardiogram recorded during the

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first 3 days of infarction (p < 0.0005). Sudden death was only predicted by left ventricular ejection fraction (p <0.02). These data suggest that the degree of myocardial damage as assessed by left ventricular ejection fraction is the strongest predictor of sustained ventricular arrhythmias during follow-up and the only predictor of sudden cardiac death after myocardial infarction. Serial recordings of the signal-averaged electrocardiogram did not give additional information as to occurrence of ventricular tachyarrhythmias or sudden death.

1203

Prognostic Value of Predischarge Low-Level Exercise Thallium **Testing After Thrombolytic Treatment of Acute Myocardial** Infarction

Peter L. Tilkemeier, Timothy E. Guiney, Paul J. LaRaia, and Charles A. Boucher

Predischarge low-level exercise thallium testing has been used to assess patient prognosis after acute myocardial infarction (AMI). Sixty-seven patients after reperfusion therapy for AMI and 107 patients without acute intervention were evaluated with predischarge low-level exercise thallium testing and followed for a mean of 367 days for repeat cardiac events. STsegment depression and increased lung uptake were prognostic predictors in the nonintervention group and reversible left ventricular cavity dilatation was significant in the intervention group. Exercise thallium imaging detected 81% of events in the nonintervention group and 55% in the intervention group. This suggests an unstable coronary artery lesion or progression of disease as a cause for a cardiac event; however, neither of these were adequately assessed by predischarge low-level exercise thallium imaging. Tests presumed to be useful after an AMI may not have similar prognostic usefulness after acute intervention after an AMI.

Prognosis of Acute Myocardial Infarction Complicated by Primary Ventricular Fibrillation

Solomon Behar, Uri Goldbourt, Henrietta Reicher-Reiss, Elieser Kaplinsky, and the Principal Investigators of the SPRINT Study

In 5,839 consecutive patients with acute myocardial infarction, the incidence of primary ventricular fibrillation (VF) was 2.1%. Patients with primary VF resembled counterparts without ventricular VF. In-hospital mortality rate was 18.8% in 122 patients with primary VF compared with 8.5% in 3,707 patients forming the reference group (p <0.01). Adjustment by gender, history of myocardial infarction, systemic hypertension and by enzymatically estimated infarct size yielded relative mortality odds of 2.52 (95% confidence interval, 1.42 to 4.46). Prognosis after discharge from the hospital was independent of primary VF.



ADD CAPOTEN EARLY



IN MILD, MODERATE, AND SEVERE HEART FAILURE (NYHA Class II, III, and IV)



*CAPOTEN is indicated in patients with heart failure who have not responded adequately to treatment with diuretics and digitalis. Although the beneficial effect of captopril in heart failure does not require the presence of digitalis, most controlled clinical trial experience with captopril has been in patients receiving digitalis as well as diuretic treatment. Consequently, CAPOTEN should generally be added to both of these agents except when digitalis use is poorly tolerated or otherwise not feasible. In using CAPOTEN, consideration should be given to the risk of neutropenia/agranulocytosis. Use special precautions in patients with impaired renal function, collagen vascular disorders, or those exposed to other drugs known to affect the white blood cells or immune response. Evaluation of heart failure patients should always include assessment of renal function. See INDICATIONS, CONTRAINDICATIONS, WARNINGS, and ADVERSE REACTIONS in the brief summary on adjacent page.

CAPOTEN® TABLETS **Captopril Tablets**

INDICATIONS: Hypertension-CAPOTEN (captopril) is indicated for the treatment of hyper tension. Consideration should be given to the risk of neutropenia/ agranulocytosis (see WARN-INGS). CAPOTEN is effective alone and in combination with other antihypertensive agents, especially thiazide-type diuretics

Heart Failure: CAPOTEN (captopril) is indicated in the treatment of congestive heart fa patients who have not responded adequately to treatment with diuretics and digitalis. CAPOTEN should generally be added to both of these agents except when digitalis use is poorly tolerated or otherwise not feasible

CONTRAINDICATIONS: CAPOTEN is contraindicated in patients who are hypersensitive to this product

WARNINGS: Angioedema—Angioedema involving the extremities, face, lips, mucous membranes, tongue, glottis or larynx has been seen in patients treated with ACE inhibitors, including captopril. If angioedema involves the tongue, glottis or larynx, airway obstruction may occur and be fatal. Emergency therapy, including but not necessarily limited to, subcutaneous administration of a 1:1000 solution of epinephrine should be promptly instituted.

Neutropenia/Agranulocytosis—Neutropenia (<1000/mm³) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine less than 1.6 mg/dL and no collagen vascular disease), neutropenia has been seen in one patient out of over 8,600 exposed. In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk in clinical trials was about 1 per 500. Doses were relatively high in these patients, particularly in view of their diminished renal function. In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during the subsequent clinical experience. Of reported cases, about half had serum creatinine ≥ 1.6 mg/dL and more than 75% received procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

Neutropenia has appeared usually within 3 months after starting therapy, associated with myeloid hypoplasia and frequently accompanied by erythroid hypoplasia and decreased num-bers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen. Neutrophils generally returned to normal in about 2 weeks after captooril was discontinued, and serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities ere in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors. Evalua tion of the hypertensive or heart failure patient should always include assessment of renal function. If captopril is used in patients with impaired renal function, white blood cell and ial counts should be evaluated prior to starting treatment and at approximately 2-week intervals for about 3 months, then periodically. In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever). If infection is suspected, perform white cell counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count < 1000/mm³) withdraw captopril and closely follow the patient's course.

Proteinuria: Total urinary proteins >1 g per day were seen in about 0.7% of patients on captopril. About 90% of affected patients had evidence of prior renal disease or received high doses (>150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients. Since most cases of proteinuria occurred by the 8th month of therapy with captopril, patients with prior renal disease or those receiving captopril at doses >150 mg per day, should have urinary protein estimates (dip-stick on 1st morning urine) before therapy, and periodically thereafter.

Hypotension: Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]). In heart failure, where the blood pressure was either normal or low, transient decreases in mean blood pressure >20% were recorded in about half of the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whene ever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

PRECAUTIONS: General: Impaired Renal Function—Hypertension—Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure-About 20% of patients develop stable elevations of BUN and serum creatinine >20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. Valvular Stenosis—A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis due to decreased afterload reduction. Surgery/Anesthesia-If hypotension occurs during surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Drug Interactions: Hypotension-Patients on Diuretic Therapy-Precipitous reduction of blood pressure may occasionally occur within the 1st hour after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretics, and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy or by initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least 1 hour after the initial dose.

Agents Having Vasodilator Activity-In heart failure patients, vasodilators should be a ministered with caution.

Agents Causing Renin Release-Captopril's effect will be augmented by antihypertensive agents that cause renin release

Agents Affecting Sympathetic Activity-The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the

overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g.,

ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium—Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Use potassium-containing salt substitutes with caution.

Inhibitors of Endogenous Prostaglandin Synthesis—Indomethacin and other nonstroidal anti-inflammatory agents may reduce the antihyperlensive effect of captopril, especially in low renin hypertension.

Lithium-Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy. These drugs should be coadministered with caution and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, it may increase the risk of lithium toxicity.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility. Pregnancy: Category C: Embryocidal effects and craniofacial malformations were observed in

rabbits. Human Experience—There are no adequate and well-controlled studies of captopril in pregnant women. Data are available that show captopril crosses the human placenta. Captopril nould be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Based on post-marketing experience with all ACE inhibitors, the following information has

been collected. Inadvertent exposure limited to the first trimester of pregnancy does not appear to affect fetal outcome adversely. Fetal exposure during the second and third trimester of pregnancy has been associated with fetal and neonatal morbidity and mortality.

When ACE inhibitors are used during the later stages of pregnancy, there have been reports of hypotension and decreased renal perfusion in the newborn. Oligohydramnios in the mother has also been reported. Infants exposed in utero to ACE inhibitors should be closely observed. for hypotension, oliguria and hyperkalemia. If cliguria occurs, attention should be directed toward support of blood pressure and renal perfusion with the administration of fluids and pressors as appropriate. Problems associated with prematurity such as patent ductus arterisus have occurred in association with maternal use of ACE inhibitors but it is not clear whether they are related to ACE inhibition, maternal hypertension or the underlying prematurity

There is no experience with exchange transfusion, hemodialysis or peritoneal dialysis for removing captopril from the neonatal circulation.

Nursing Mothers: Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving approxitely 7000 patien

Renal—About 1 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients

Hematologic-Neutropenia/agranulocytosis has occurred (see WARNINGS). Anemia

thrombocytopenia, and pancytopenia have been reported.

*Dermatologic**—Rash, (usually maculopapular, rarely urticarial), often with pruritus, and some times with fever and eosinophilia, in about 4 to 7 of 100 patients (depending on renal status and dose), usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients tients. A reversible associated pemphigoid-like lesion, and photosensitivity, have also been reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular—Hypotension may occur; see WARNINGS and PRECAUTIONS [Drug Interactions] for discussion of hypotension on initiation of captopril therapy. Tachycardia, ches pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia—Approximately 2 to 4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually

self-limited even with continued drug use (2 to 3 months).

Angioedema—Angioedema involving the extremities, face, lips, mucous membranes, tongue glottis or larynx has been reported in approximately one in 1000 patients. Angioedema involving the upper airways has caused fatal airway obstruction. (See WARNINGS.)

The following have been reported in about 0.5 to 2 percent of patients but did not appear a increased frequency compared to placebo or other treatments used in controlled trials: gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, cough, alo

Other Clinical adverse effects reported since the drug was marketed are listed below by body system. In this setting, an incidence or causal relationship cannot be accurately determined. General: Asthenia, gynecomastia.

Cardiovascular: Cardiac arrest, cerebrovascular accident, syncope.

Dermatologic: Bullous pemphigus. Gastrointestinal: Pancreatitis, glossitis.

Hematologic: Anemia, including aplastic and hemolytic.

Hepatobiliary: Hepatitis, including rare cases of necrosis, cholestasis.

etabolic: Symptomatic hyponatremia Musculoskeletal: Myalgia, myasthenia.

Nervous/Psychiatric: Ataxia, confusion, depression, nervousness, somnolence.

Respiratory: Bronchospasm, eosinophilic pneumonitis, rhinitis. Special Senses: Blurred vision. Urogenital: Impotence. As with other ACE inhibitors, a syndrome has been reported which includes: fever, myalgia arthralgia, rash or other dermatologic manifestations, ecsinophilia and an elevated ESR. Find

ings have usually resolved with discontinuation of treatment. Altered Laboratory Findings: Serum Electrolytes: Hyperkalemia: small increases in serum pot tassium, especially in patients with renal impairment (see PRECAUTIONS).

Hyponatremia: particularly in patients with renal impairment (see Fricard Inches).

Hyponatremia: particularly in patients receiving a low sodium diet or concomitant diuretics
BUN/Serum Creatinine: Transient elevations of BUN or serum creatinine especially in volum
or salt depleted patients or those with renovascular hypertension may occur. Rapid reduction
of longstanding or markedly elevated blood pressure can result in decreases in the glomerula

filtration rate and, in turn, lead to increases in BUN or serum creatinine.

Hematologic: A positive ANA has been reported.

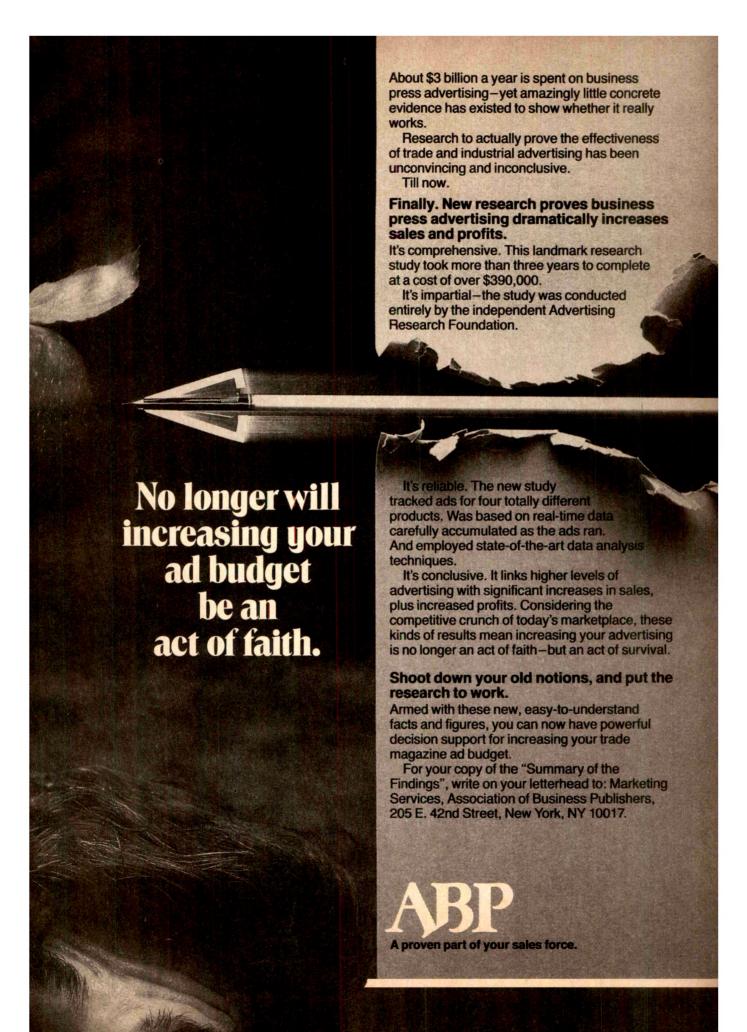
Liver Function Tests: Elevations of liver transaminases, alkaline phosphatase, and serur bilirubin have occurred.

OVERDOSAGE: Primary concern is correction of hypotension. Volume expansion with an I. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopr may be removed from the general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: CAPOTEN (captopril) should be taken one hour before me In hypertension, CAPOTEN may be dosed bid or tid. Dosage must be individualized; see DOS AGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily be the kidneys, dosage adjustments are recommended for patients with impaired renal function

Consult package insert before prescribing CAPOTEN (captopril).

HOW SUPPLIED: Available in tablets of 12.5, 25, and 50 mg in bottles of 100 and 1000; 100 m in bottles of 100; and in UNIMATIC* unit-dose packs of 100 tablets. (J3-658f



ARRHYTHMIAS AND CONDUCTION DISTURBANCES

Usefulness of Labetalol in Chronic Atrial Fibrillation

Cheuk-Kit Wong, Chu-Pak Lau, Wing-Hung Leung, and Chun-Ho Cheng

We studied the effect of labetalol in 10 patients with chronic atrial fibrillation (AF) without structural heart disease. Labetalol did not reduce exercise tolerance. Digoxin was inefficacious in controlling maximal heart rate during treadmill tests but labetalol, both when used alone or as an adjunct to digoxin, was advantageous (156 \pm 4 vs 177 \pm 2 beats/min, p <0.01, and 154 ± 4 vs 177 ± 2 beats/min, p <0.01, respectively). The ratepressure products were consistently lowered by labetalol at rest and during exercise. During submaximal exercise on treadmill tests or during 12minute walks, the combination of labetalol and digoxin produced the best heart rate control, whereas heart rate control with labetalol monotherapy was comparable to that with digoxin monotherapy. During daily activities, the addition of labetalol to digoxin improved control of maximal heart rate $(141 \pm 5 \text{ vs } 172 \pm 5 \text{ beats/min}, p < 0.01)$ without causing bradycardia. Labetalol is thus useful in chronic AF.

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Usefulness of Combined Propranolol and Verapamil for Evaluation of Surgical Ablation of Accessory Atrioventricular Connections in Patients Without Structural Heart Disease

Simón Milstein, Ann Dunnigan, Jeffrey Buetikofer, David G. Benditt, Jane Crosson, and Edgar Pineda

Successful surgical ablation of atrioventricular (AV) accessory connections may be difficult to confirm during postoperative evaluation due to the presence of enhanced retrograde AV nodal conduction. Drugs selectively affecting AV nodal conduction and refractoriness with no effects on accessory connection may be helpful for assessing the success of the surgical procedure. Combined intravenous propranolol and verapamil were given pre- and postoperatively in 17 patients undergoing surgical ablation of accessory connection. In all but 1 of the accessory connections, conduction and refractoriness were unaffected. In contrast, postoperative evaluation revealed significant prolongation of AV nodal conduction and refractoriness. Thus, the combined administration of propranolol and verapamil may prove helpful for differentiating between AV nodal and residual accessory connection conduction during early postoperative assessment of patients undergoing surgery for accessory AV connection ablation.

Long-Term Effect of Mexiletine on Left Ventricular Function and Relation to Suppression of Ventricular Arrhythmia

Steven Singh, Richard Klein, Brian Eisenberg, Edward Hughes, Margaret Shand, and Pat Doherty, with the technical assistance of Gerhard Sharon

The effects of oral mexiletine on left ventricular ejection fraction (LVEF) and ventricular arrhythmias were evaluated during 3 months of therapy in

Continued on page A33

CLOSELY STUDIED WIDELY USED HIGHLY EFFECTIVE

For many patients with primary hypercholesterolemia (Types IIa and IIb), when diet and other nondrug therapies are inadequate

MEVACOR® (LOVASTATIN | MSD)



MEVACOR is contraindicated in patients who are hypersensitive to any component of the medication; in patients with active liver disease or unexplained persistent transaminase elevations; in pregnant or lactating patients; and in women of childbearing age, except when such patients are highly unlikely to conceive.

It is recommended that liver function tests be performed before treatment begins, every 4 to 6
weeks during the first 15 months of therapy, and periodically thereafter in all patients. Special
attention should be paid to patients who develop elevated serum transaminase levels, and in these
patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to three times the upper limit of
normal and are persistent, the drug should be discontinued.

For complete details on MEVACOR, including cautionary information regarding myopathy, drug interactions, and slit-lamp monitoring, please refer to the Prescribing Information.

For a Brief Summary of Prescribing Information, please see the back of this advertisement.







mg

Also available as a 40-mg tablet

CONTRAINDICATIONS: Hypersensitivity to any component of this

Active liver disease or unexplained persistent elevations of serum transaminases.
Pregnancy and lactation

Pregnancy and lactation.

Atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Moreover, cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development, including synthesis of steroids and cell membranes. Because of the ability of inhibitors of HMG-CoA reductase such as MEVACOR® (Lovastatin, MSD) to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway, MEVACOR may cause fetal harm when administered to a pregnant woman. Therefore, lovastatin is contraindicated during pregnant which such patients are highly unlikely to conceive. If the patient becomes pregnant while taking this orru, lovastatin should be discontinued and the patient should be apprised of the potential hazard to the fetus.

WARNINGS: Liver Dysfunction: Marked persistent increases (to more than 3 times the upper limit of normal) in serum transaminases occurred in 1.9% of adult patients who received lovastatin for at least one year in clinical trials (see ADVERSE REACTIONS). When the drug cocurred in 1.9% of adult patients who received lovastatin for at least one year in clinical trials (see ADVERSE REACTIONS). When the drug was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pretreatment levels. The increases usually appeared to 10 to 20 months after the start of therapy with lovastatin and were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity. A liver biopsy was done in one of these patients and showed areas of focal hepatitis. In this patient, transaminase levels returned to normal following discontinuation of therapy. Some of these patients had abnormal liver function tests prior to lovastatin therapy and/or consumed substantial quantities of alcohol.

It is recommended that liver function tests be performed before treatment begins, every 4 to 6 weeks during the first 15 months of therapy with lovastatin, and periodically thereafter in all patients. Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rase to 3 times the upper limit of normal and are persistent, the drug should be discontinued. Liver biopsy should be considered if elevations are persistent beyond the discontinuation of the drug.

The drug should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver diseases or unexplained transaminase levels shows a substantial quantities of alcohol and/or have a past history of liver disease has the proposition of the drug.

As with other lipid-lowering agents, moderate (less than 3 times the upper limit of normal) elevations of serum transaminases have been reported following therapy with MEVACOR (see ADVERSE REACTIONS). These changes appeared soon after initiation of therapy with MEVACOR we

These changes appeared soon after initiation of therapy with MEVACOR, were often transient, were not accompanied by any symptoms, and interruption of treatment was not required.

Skeletal Muscle: Several cases of rhabdomyolysis have been associated with lovastatin therapy alone, when combined with immunosuppressive therapy including cyclosporine in cardiac transplant patients, and when combined in non-transplant patients with either gemilibrozii or lipid-lowering dosse; 2: gloday) of nicollinic acid. Acute renal failure from rhabdomyolysis is have been seen more commonly with the lovastatin-gemilibrozii combination and has also been reported in transplant patients receiving lovastatin plus cyclosporine.

Rhabdomyolysis with or without renal impairment has been reported in seriously ill patients receiving cythromycin concomitantly with lovastatin. Therefore, patients receiving concomitant lovastatin and crythromycin should be carefully monitored.

Fulminant rhabdomyolysis has been seen as early as 3 weeks after initiation of combined therapy with gemilibrozil and lovastatin but may be seen after several months. For these reasons, it is felt that, in most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefits of combined therapy with ovastatin and gemilibrozil do not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. While it is not known whether this interaction occurs with fibrates other than gemilibrozil, myopathy and rhabdomyolysis have occasionally been associated with the use of other librates alone, including clofibrate. Therefore, the combined use of lovastatin with other fibrates should generally be avoided.

Physicians contemplating combined therapy with lovastatin and lipid-lowering doses of nicotinic acid or with immunosuppressive drugs should carefully weigh the potential benefits and risks and should carefully mention patients for any signs and symptoms of muscle pain tenderness, or weakness, particularly during the initial mon

discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Most of the patients who have developed myopathy (including rhabdomyolysis) while taking lovastatin were receiving concomitant therapy with immunosuppressive drugs, gemfibrozil, or lipid-lowering doses of nicotinic acid. In clinical trials, about 30% of patients on concomitant immunosuppressive therapy including cyclosporine developed myopathy, the corresponding percentages for gemfibrozil and niacin were approximately 5% and 2%, respectively. In 6 patients with cardiac transplants taking immunosuppressive therapy including cyclosporine concomitantly with lovastatin 20 mg/day, the average plasma level of active metabolites derived from lovastatin was elevated to approximately 4 times the expected levels. Because of an apparent relationship between increased plasma levels of active metabolites derived from lovastatin and myopathy, the daily dosage in patients taking immunosuppressants should not exceed 20 mg/day (see DOSAGE AND ADMINISTRATION). Even at this dosage, the benefits and risks of using lovastatin in patients taking immunosuppressants should be carefully

PRECAUTIONS: General: Before instituting therapy with MEVACOR® (Lovastatin, MSD), an attempt should be made to control hypercholesterolem with appropriate dief, exercise, weight reduction in obese patients and to treat other underlying medical problems (see INDICATIONS AND

USAUC).

Lovastatin may elevate creatine phosphokinase and transaminase levels (see ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with lovastatin.

Eye: There was a high prevalence of baseline lenticular opacities in the

Eye: There was a high prevalence of baseline ienticular opacities in the patient population included in the clinical trials with lovastain. During these trials the appearance of new opacities was noted. The causal relationship of lovastain to these findings has not been established. Of 431 patients examined with slit lamp at baseline and during therapy with lovastat n, 34 had opacities reported at the final examination (5 to 15 months after starting lovastatin) that were not noted at baseline. On the other hand, in 45 patients, opacities observed at baseline were not noted at the final examination, so that theprevalence did not increase. There was no clinically significant change in visual acuity in the patients who had new opacities reported, nor was any patient, including those with opacities noted at baseline, discontinued from therapy because of a decrease in visual acuity. Nevertheless, until further experience is obtained, it is recommended that patients placed on lovastain therapy be examined with a slit lamp before or shortly after initiation of treatment and annually thereafter.

Homozygous Familial Hypercholesterolemia: MEVACOR is less effective in patients with the rare flomozygous familial hypercholesterol-emia, possibly because these patients have no functional LDL receptors. MEVACOR appears to be more likely to raise serum transaminases (see ADVERSE REACTIONS) in these homozygous patients.

MEVACOR appears to be more likely to raise serum transaminases (see ADVERSE REACTIONS) in these homozygous patients.

Drug Interactions: Immunosuppressive Drugs, Gemtibiozii, Niacin (Nicotinic Acid), Erythromycin: See WARNINGS, Skeletal Muscle.

Coumarin Anticoagulants: In a clinical trial in warfarin-treated patients designed specifically to observe a potential effect of lovastatin on the prothrombin time, lovastatin in dosages up to 40 mg b.i.d. did not produce any consistent alteration of the anticoagulant action of warfarin. However, since the drug was marketed, clinically evident bleeding and/or increased prothrombin time have been reported in a few patients taking coumarin anticoagulants concomitantly with lovastatin. The causal relationship to lovastatin is unclear. Nevertheless, it is recommended that in patients taking anticoagulants, prothrombin time be determined before starting lovastatin and frequently enough during early therapy to insisue that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. Antipyrine is a model for drugs metabolized by the microsomal hepatic enzyme system (cytochrome P450 system). Because lovastatin had no effect on the pharmacokinetics of antipyrine, interactions with other drugs metabolized via this mechanism are not expected. Propranolol: In normal volunteers, there was no clinically significant pharmacokinetics or harmacodynamic interaction with concomitant administration of single doses of lovastatin and propranolol. Digozin: In patients with hypercholesterolemia, concomitant administration of single doses of lovastatin and propranolol.

Other Concomitant Therapy: Although specific interaction studies were

concentrations

Other Concomitant Therapy: Although specific interaction studies were not performed, in clinical studies, lovastatin was used concomitantly with beta blockers, calcium channel blockers, diuretics, and nonsteroidal anti-inflammatory drugs (NSAIDs) without evidence of clinically significant adverse interactions.

adverse interactions

**Carcinogenesis, Mutagenesis, Impairment al Fertility:* In a 21-month carcinogenic study in mice, a statistically significant (p=0.05) increase in the incidence of hepatocellular carcinomas and adenomas was observed at doses of 500 mg/kg/day (312 times the maximum recommended human dose) of lovastatin. These changes were not seen in mice given doses of 20 and 100 mg/kg/day (12.5 and 62.5 times the maximum recommended human dose).

A statistically significant increase (p > 0.05) in the incidence of pulmonary adenomas was seen in female mice receiving 500 mg/kg/day (312 times the maximum recommended human dose): no similar changes were seen in males at any dose or in females receiving 20 or 100 mg/kg/day (12.5 or 62.5 times the maximum recommended human dose). Because the incidence of pulmonary tumors was within the range of untreated animals in studies of similar duration, the relationship of this latter change to treatment is not known.

cause the incidence of pulmorally fullions was within the range of untreated animals in studies of similar duration, the relationship of this latter change to treatment is not known. In addition, an increase in the incidence of papilloma in the non-glandular mucosa of the stomach was observed in mice receiving 100 and 500 mg/kg/day (62.5 and 312 times the maximum recommended human dose). The glandular mucosa was not affected. The human stomach contains only glandular mucosa importantly, there is a strong association between this change and hyperplasia of the squamous epithelium (acanthosis) in this region; acanthosis is a characteristic change observed in the non-glandular mucosa of rodents treated with HMG-CoA reductase inhibitors and is most probably a result of inhibition of the reductase in this tissue.

Similar squamous epithelium is found in the esophagus and anorectal junction of the mouse and rat, however, no evidence of a similar drug-induced hyperplastic response was observed in these tissues in studies of up to 21 months in the mouse given up to 500 mg/kg/day (312 times the maximum recommended human dose), or in a study of 24 months in the rat given 180 mg/kg/day (112 times the maximum recommended human dose).

In a 24-month carcinogenicity study in rats, there was a positive dose response relationship for hepatocellular carcinogenicity in males (unad-justed p = 0 025). However, because the incidence of hepatocellular car-cinogenicity observed in male rats in this study is similar to that observed spontaneously in this strain of rat, the implications of this finding are

unclear
No evidence of mutagenicity was observed in a microbial mutagen test
using mutant strains of Salmonella typhimuium with or without rat or
mouse liver metabolic activation. In addition, no evidence of damage to
genetic material was noted in an in vitro alkaline elution assay using rat or
mouse hepatocytes, a V-79 mammalian cell forward mutation study, an in
vitro chromosome aberration study in CHO cells, or an in vivo chromosomal aberration assay in mouse bone marrow.
No drug-related effects on fertility were found in studies with rats.

No drug-related effects on tertility were found in studies with rats.

Pregnancy: Pregnancy Category X: See CONTRAINDICATIONS.

Lovastatin has been shown to produce skeletal malformations in the rat fetus at doses of 800 mg/kg/day (500 times the maximum recommended human dose). At similar doses in mice, an increase in skeletal malformations was observed. These individual changes are within the range of those observed spontaneously in this strain of mouse. No drug-induced changes were seen in either species at doses of up to 80 mg/kg/day (50 times the maximum recommended human dose). No evidence of malformations was noted in rabbits at up to 15 mg/kg/day (highest tolerated dose about 9 times the maximum recommended human dose). There are no data in pregnant women. data in pregnant women.

Nursing Mathers: Studies in rats have shown that lovastatin is excreted in Nursing Mothers: Studies in rasmave shown that to vastation become the milk. It is not known whether this drug is excreted in human milk Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from MEVACOR. women taking lovastatin should not nurse their infants (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in children have not been established. Because children are not likely to benefit from cholesterol lowering

studies in subjects below the age of 20 years), treatment of children with lovastatin is not recommended at this time.

ADVERSE REACTIONS: MEVACOR® (Lovastatin, MSD) is generally well ADVERSE REACTIONS: MEVACOR® (Lovastatin, MSD) is generally well telerated; adverse reactions usually have been mild and transient. Less than 1% of patients were discontinued from controlled clinical studies due to adverse experiences attributable to MEVACOR. About 2% of patients were discontinued from all studies (controlled and uncontrolled) due to adverse experiences attributable to MEVACOR; about one-third of these patients were discontinued due to increases in serum transaminases.

Clinical Adverse Experiences: Adverse experiences reported in patie reated with MEVACOR in controlled clinical studies are shown in the table

	MEVACOR (N = 613)	Placebo (N = 82)	Cholestyramine (N = 88) %	Probuco (N = 97) %
Gastrointestinal				
Constipation	4.9	_	34.1	2.1
Diarrhea	5.5	4.9	8.0	10.3
Dyspepsia	3.9	_	13.6	3.1
Flatus	6.4	2.4	21.6	2.1 5.2
Abdominal pain/cramps		2.4	5.7	5.2
Heartburn	1.6	_	8.0	_
Nausea	4.7	3.7	9.1	6.2
Musculoskeletal				
Muscle cramps	1.1	_	1.1	_
Myalgia	2.4	1.2	_	_
Nervous System/Psychiatric				
Dizziness	2.0	12	_	1.0
Headache	9.3	4.9	4.5	1.0
Skin	5.0			
Rash/pruritus	5.2	_	4.5	_
Special Senses	0.2		1.0	
Blurred vision	1.5	_	1.1	3.1
Dysgeusia	0.8	_	1.1	_

Laboratory Tests. Marked persistent increases of serum transaminases have been noted (see WARNINGS).

About 11% of patients had elevations of creatine phosphokinase (CPK) levels of at least twice the normal value on one or more occasions. The corresponding values for the control agents were cholestyramine. 9% and probuod), 2%. This was attributable to the noncardiac fraction of CPK Large increases in CPK have sometimes been reported (see WARNINGS. Skeletal Muscle).

Concomitant Therapy: In controlled clinical studies in which lovastating Concomitant Therapy: In controlled clinical studies in which lovastatin was administered concomitantly with cholestyramine, no adverse reactions peculiar to this concomitant treatment were observed. The adverse reactions that occurred were limited to those reported previously with lovastatin or holestyramine. Other lipid-lowering agents were not administered concomitantly with lovastatin during controlled clinical studies. In uncontrolled clinical studies, most of the patients who have developed myopathy were receiving concomitant therapy with immunosuppressive drugs, gentifibrozil, or niacin (nicotinic acid) (see WARNINGS, Skeleta Muscie)

Uncontrolled Clinical Studies: The adverse experiences observed ir uncontrolled studies were similar to those seen in controlled clinica studies. Abnormal inverfunction tests were observed at a higher incidence than in the controlled studies (see WARNINGS, Liver Dysfunction). Myop athy (myagipa with marked CPK elevations) was reported in approximately 0.5% of patients (see WARNINGS, Skeletal Muscle).

Causal Relationship Unclear: Nervous System: Peripheral neuropath has been reported: the relationship to lovastatin is uncertain. Visua evoked response. nerve conduction measurements, and electromyography in over 30 patients showed no evidence of neurotoxic effects o

vastatin. Special Senses: Of 431 patients examined with slit lamp at baseline and Special Senses: 01 451 patients examined with six lamp at baseline and during therapy with lovastatin, 34 had popatities reported at the final examination (5 to 15 months after starting lovastatin) that were not noted a baseline. On the other hand, in 45 patients, opacities observed at baselin were not noted at the final examination, so that the prevalence did no increase (see PRECAUTIONS).

Post-marketing Experience: Additional adverse experiences occurring

nce the drug was marketed are listed below:

Clinical Adverse Experiences

Gastrointestinal: Hepatitis cholestatic jaundice, anorexia

Gastrointestinal: Hepatitis cholestatic jaundice, anorexia vomiting. Hypersensitivity/Reactions: An apparent hypersensitivity syndrom has been reported rarely which has included one or more of the followin leatures: anaphyaxis, angioederma. Jupus-like syndrome, polymyalgi rheumatica, thrombocytopenia, leukopenia, hemolytic anemia, positiv ANA, ESR increase, arrhntis, arthralgia, urticaria, asthenia, photosensi livity, lever, flushing, malaise, and dyspnea. Hervous Systemi/Psychiatric: Psychic disturbances, includin anxiety anesthesia.

anxiety; paresthesia.

Causal Relationship Unknown

Gastrointestinal Pancreatitis, stomatitis.

Skin: Alopecia.

Nervous System/Psychiatric: Depression, insomnia.

Metabolic: Edema.

Metabolic: Edema.

Clinical Laboratory Test Findings
Liver Function Tests. Liver function test abnormalities, includin
elevated alkaline phosphatase and bilirubin.

Thyroid Function Tests. Fare reports of thyroid function test abno
malities in patients taking concomitant thyroxine.

OVERDOSAGE: The oral LO₅₀ of MEVACOR in mice is 20 g/kg. Five healthy human volunteers have received up to 200 mg of lovastat as a single dose without clinically significant adverse experiences. A fe cases of accidental overdosage have been reported: no patients had ar specific symptoms, and all patients recovered without sequelae. The ma:

imum dose taken was 5 to 6 g.
Until further experience is obtained, no specific treatment of overdo:
age with MEVACOR can be recommended.

The dialyzability of levastatin and its metabolites in man is not known

present.

DOSAGE AND ADMINISTRATION: The patient should be placed on a state dard cholesterol-lowering diet before receiving MEVACOR and shou continue on this diet during treatment with MEVACOR. MEVACOR shou be given with meals.

The recommended starting dose is 20 mg once a day given with the evening meal. The recommended dosing range is 20 to 80 mg day in sigle or divided doses; the maximum recommended dose is 80 mg da Adjustments of cosage should be made at intervals of 4 weeks or mor Doses should be individualized according to the patient's response (s Tables 1 to IV under CLINICAL PHARMACOLOGY Clinical Studies for do response resoults).

response results).

For those patients with severely elevated serum cholesterol leve (i. e., >300 mg/dL [7.8 mmol/L] on diet), MEVACOR may be initiated at a

mg/day mg/day.

In patients taking immunosuppressive drugs concomitantly wi lovastatin (see WARNINGS. Skeletal Muscle), the maximum recormended dosage is 20 mg/day.

Cholesterol levels should be monitored periodically and considerationable of the provided of the consideration of the consi

MERO SHAR DOHN

For more detailed information, consult your MSD Representative or s Prescribing Information, Merck Sharp & Dohme, Division of Merck

ONTENTS/ABSTRACTS

29 patients with chronic ventricular premature complexes (VPCs) and a mean LVEF of 46% by 24-hour Holter monitoring and radionuclide ventriculography at rest and during maximum tolerable exercise testing. At the end of titration and after 3 months of therapy, patients with a baseline LVEF ≤40% (group 2) responded with a median reduction of the hourly VPC rate by 90 and 81%, respectively, compared with 79 and 72% in those with a baseline LVEF >40% (group 1). Couplets and runs of ventricular tachycardia were almost completely suppressed in nearly all patients. One patient had a proarrhythmic increase in VPCs during treatment. There were no significant changes in resting or exercise LVEF after treatment in either of the 2 groups. No symptoms of congestive heart failure developed.

SYSTEMIC HYPERTENSION

1228

Effectiveness of the Once-Daily Calcium Antagonist, Lacidipine, in Controlling 24-Hour Ambulatory Blood Pressure

Mary E. Heber, Paul A. Broadhurst, Geoffrey S. Brigden, and Edward B. Raftery

The efficacy of the new once-daily dihydropyridine calcium antagonist lacidipine in reducing ambulatory intraarterial blood pressure was assessed in 12 untreated hypertensive patients. Chronic administration reduced blood pressure throughout the 24-hour period. In addition, there was no postural hypotension and there was successful attenuation of the pressor response to isometric and dynamic exercise.

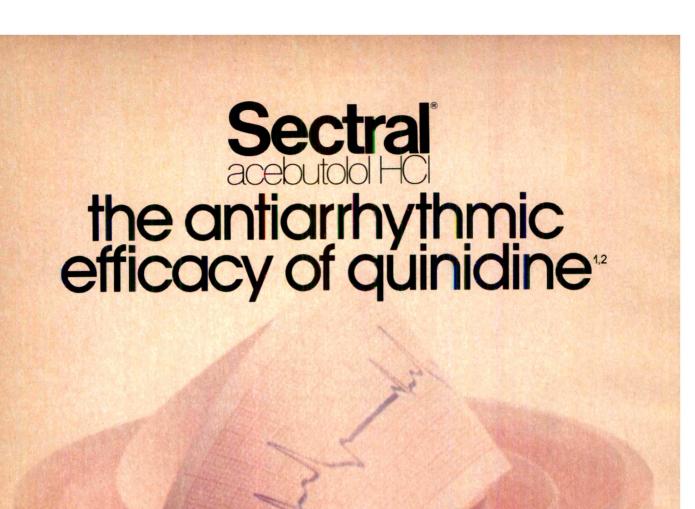
CONGENITAL HEART DISEASE

Atenolol Therapy for Exercise-Induced Hypertension After **Aortic Coarctation Repair**

Rae-Ellen W. Kavey, John L. Cotton, and Marie S. Blackman

Ten patients with exercise-induced upper body systolic hypertension after successful surgical repair of coarctation in childhood were evaluated by treadmill exercise before and after β blockade with atenolol. At rest, arm/ leg systolic pressure difference was ≤18 mm Hg in all. At baseline treadmill evaluation, systolic blood pressures at exercise termination ranged from 201 to 270 mm Hg (mean 229) and arm/leg gradients ranged from 30 to 143 mm Hg (mean 84). After β blockade, upper extremity systolic pressures at exercise termination were normalized in 9 of 10 patients (range 163 to 223 mm Hg; mean 196, p ≤0.005). Arm/leg gradient also decreased significantly with a mean of 51 mm Hg (p ≤0.05). No patient had symptoms on atenolol and exercise endurance times were unchanged. There is a high incidence of premature cardiovascular disease after successful coarctation repair, and persistent upper body hypertension would be anticipated to contribute to this. The study results suggest that cardioselective β blockade is effective therapy in this situation.

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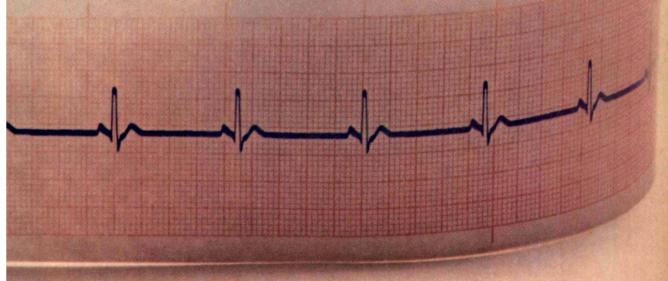
...and the safety of a beta blocker.

Sectral® (acebutolol HCI) is a beta blocker demonstrated as effective as quinidine in a wide range of premature ventricular complexes (paired and multiform ventricular ectopic beats and R-on-T beats).* Sectral® offers excellent G.I. tolerability. It does not interact with digoxin. And Sectral, like other beta blockers, is rarely associated with proarrhythmia.³

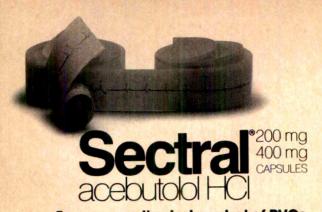
Initiate Sectral therapy with 200 mg b.i.d. Dosage can be increased gradually until optimal response is obtained, generally between 600 mg to 1200 mg per day.

*Sectral® is not indicated for ventricular tachycardia.
Please see brief summary on adjacent page.

Like other beta blockers, Sectral is contraindicated in persistently severe bradycardia, second- and third-degree heart block, overt cardiac failure or cardiogenic shock.



Sectral acebutolol HC For uncomplicated control of PVCs.



For uncomplicated control of PVCs.

(Brief Summary. See Package Circular for full prescribing information.)

CONTRAINDICATIONS: SECTRAL is contraindicated in: 1) persistently severe bradycardia; 2) second- and third-degree heart block; 3) overt cardiac failure: cardiogenic shock. (See WARNINGS)

WARNINGS: Cardiac Failure: Sympathetic stimulation may be essential for support of circulation in patients with diminished myocardial contractility, and inhibition by β-adrenergic receptor blockade may precipitate more severe failure. Although β-blockers should be avoided in overt cardiac failure, SECTRAL can be used B-blockers should be avoided in overt cardiac failure. SECTRAL can be used cautiously when heart failure is controlled with digitalis and/or diuretics. Digitalis and SECTRAL impair AV conduction. Withdraw SECTRAL if cardiac failure persists. In Patients Without a History of Cardiac Failure: In patients with aortic or mitral valve disease or compromised left ventricular function, continued depression of the myocardium with β-blockers over time may lead to cardiac failure. Digitalize patients at first signs of failure, and/or give a diuretic and observe closely. Withdraw SECTRAL if cardiac failure persists.

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal: Abrupt discontinuation of some B-blockers in coronary artery disease patients may exacerbate angina; in some cases, myocardial infarction and death have been reported. Caution such patients against interruption of therapy without a physician's advice. Even in the absence of overt ischemic heart disease, withdraw SECTRAL gradually over a period of about two weeks, observe carefully and advise patients to minimize physical activity during this time (If desired, patients may be transferred directly to comparable doses of an alternative B-blocker without interruption of β-blocking therapy). If exacerbation of angina occurs, restart full-dose anti-anginal therapy immediately and hospitalize patient until stabilized.

Peripheral Vascular Disease: β-antagonists reduce cardiac output and can precipi tate/aggravate arterial insufficiency in patients with periphera or mesenteric vascular disease. Exercise caution and observe such patients closely for progression of arterial obstruction.

Bronchospastic Diseases: Patients with Bronchospastic Disease Should, in General, Not Receive a β -Blocker. Because of its relative β -selectivity, low doses SECTRAL may be used cautiously in such patients who do not respond to, or cannot tolerate, alternative treatment.

Since β₁-selectivity is not absolute and is dose-dependent, use lowest possible.

dose of SECTRAL initially, preferably in divided doses. Make bronchodilator, e.g. the ophylline, or a β_2 -stimulant, available in advance with instructions for use. Anesthesia and Major Surgery: The necessity/desirability of withdrawing β-blockers prior to major surgery is controversial; the heart's impaired ability to respond to β-adrenergically mediated reflex stimuli may enhance the risk of excessive myocardial depression during general anesthesia. Difficulty in restarting and maintaining the heartbeat also has been reported with beta-blockers. If treatment is continued take special care when using anesthetics that depress the myocardium, use lowest possible SECTRAL dose. SECTRAL, like other β -blockers, is a competitive inhibitor of B-receptor agonists, so its effects can be reversed by cautious administration of such agents (e.g., dobutamine or isoproterenol). Symptoms of excessive vagal tone (e.g.,

agents (e.g., obbutamine or isoproteento). Synthems of excessive vagarione (e.g., profound bradycardia, hypotension) may be corrected with atropine.

Diabetes and Hypoglycemia: β-blockers may potentiate insulin-induced hypoglycemia and mask some symptoms such as tachycardia; dizziness and sweating are usually not significantly affected. Warn diabetics of possible masked hypoglycemia.

Thyrotoxicosis: β-adrenergic blockade may mask some clinical signs (tachycardia) of hyperthyroidism. Abrupt withdrawal of SECTRAL may precipitate a thyroid storm in patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Renal or Hepatic Function: While there are no U.S. studies, foreign published experience shows that acebutolol has been used successfully in chronic renal insufficiency. Acebutolol is excreted via the G.I. tract, but the cessfully in crimic terial insulficiency. According to the kidney. A linear relationship exists between renal clearance of diacetolol and creatinine clearance (Cl_{cr}): reduce daily dose of acebutolol by 50% when Cl_{cr} is less than 50 mL/min and by 75% when it is less than 25 mL/min. Use cautiously in patients with impaired hepatic function. SECTRAL has been used successfully and without problems in elderly patients in the alderly patients.

U.S. clinical trials without specific dosage adjustment. However, in the elderly, lower

O.S. clinical trials without specific dosage adjustment. However, in the erderry, lower maintenance doses may be required because bioavailability of SECTRAL and its metabolite are approximately doubled.

Information for Patients: Warn patients, especially those with evidence of coronary artery disease, against interruption or discontinuation of SECTRAL without physician supervision. Although cardiac failure rarely occurs in properly selected patients advise patients to consult a physician if signs or symptoms suggestive of impending CHF, or unexplained respiratory symptoms, develop.

Warn patients of possible severe hypertensive reactions from concomitant use of α -adrenergic stimulants, e.g., nasal decongestants used in OTC cold medicines and nasal drops

nasal drops.

Clinical Laboratory Findings: SECTRAL, like other β-blockers, has been associated with development of antinuclear antibodies (ANA). In prospective clinical trials, patients receiving SECTRAL had a dose-dependent increase in the development of positive ANA titers. Symptoms related to this laboratory abnormality were infrequent. Symptoms and ANA titers were reversible upon discontinuation of SECTRAL.

Drug Interactions: Catecholamine-depleting drugs may have additive effects when given with β-blockers. Observe patients treated with both agents closely for evidence of teachers in patients treated with both agents closely for evidence.

given with β -blockers. Observe patients treated with out agonito syncope/pre-of marked bradycardia or hypotension which may present as vertigo, syncope/pre-syncope, or orthostatic changes in blood pressure without compensatory tachycardia

Exaggerated hypertensive responses have been reported from use of β-adrenergic antagonists with a adrenergic stimulants, including those in OTC cold remedies and vasoconstrictive nasal drops. Nonsteroidal anti-inflammatory drugs may blunt antihypertensive effects of beta-blockers.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Chronic oral toxicity studies in rats and mice, at doses 15 times the maximum recommended (60 kg) human dose, did not indicate carcinogenic potential for SECTRAL. Diacetolol, the major metabolite in man, was without carcinogenic potential in rats at doses up to 1800 mg/kg/d. SECTRAL and diacetolol also had no mutagenic potential in the Ame Test. No significant impact on reproductive performance or fertility was found in rats following SECTRAL or diacetolol doses of up to 240 or 1000 mg/kg/d, respectively. **Pregnancy:** Teratogenic Effects: Pregnancy Category B: No teratogenic effects were seen in rat or rabbit reproduction studies utilizing SECTRAL doses that were. respectively, approximately 31.5 and 6.8 times the maximum recommended human dose. At this dose in the rabbit, slight fetal growth retardation was noted; t was considered to be a result of maternal toxicity (evidenced by reduced food intake, lowered rate of body weight gain, mortality). Diacetolol studies (doses up to 450 mg/kg/d in rabbits and up to 1800 mg/kg/d in rats) showed no evidence of fetal harm other than a significant elevation in postimplantation loss with 450 mg/kg/d, a level at which food consumption and body weight gain were reduced in rabbit dams; there was a non-statistically significant increase in incidence of bilateral cataract in rat fetuses from dams treated with 1800 mg/kg/d. There are no adequate and well-controlled trials in pregnant women; SECTRAL should be used during pregnancy on if potential benefit justifies risk to the fetus

Nonteratogenic Effects: Human studies indicate that acebutolol and diacetolol cross the placenta. Neonates of mothers who received acebutolol during pregnancy have reduced birth weight, decreased blood pressure, and decreased heart rate. **Labor and Delivery**: Effect on labor and delivery in pregnant women is unknown. Anim studies have shown no effect of SECTRAL on the usual course of labor and delivery.

Nursing Mothers: Acebutolol and diacetolol appear in breast milk (milk:plasma ratio of 71 and 12.2, respectively). Use in nursing mothers is not recommended.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: SECTRAL is well tolerated in properly selected patients.

Most adverse effects have been mild, not required therapy discontinuation, and tended to decrease as treatment duration increases.

The incidence of treatment-related side effects (volunteered and elicited) derived

from U.S. controlled clinical trials in patients with hypertension, angina and arrhythm follows. Numbers represent percentage incidence for SECTRAL (N = 1002) versus

placebo (N = 314), respectively.

Cardiovascular: Chest pain 2%, 1%: Edema 2%, 1%. CNS: Depression 2%, 1%:

Dizziness 6%, 2%: Fatigue 11%, 4%: Headache 6%, 4%: Insomnia 3%, 1%: Abnormateriams 2%, 1%. Dermatelogic: Rash 2%, 1%. Gastrointestinal: Constipation 4%, 0% dreams 2%, 1%. Dermatologic. Hash 2%, 1%. Gastrointestinal. Constipation 4%, 0%. Genitour ary: Micturition (frequency) 3%, <1%. Musculoskeletal: Arthralgia 2%. 2%; Myalgia 2%, 0%. Respiratory: Cough 1%, 0%: Dyspnea 4%, 2%; Rhinitis 2%, <1%. Special Senses: Abnormal Vision 2%. 0%.

The following selected (potentially important) side effects were seen in up to 2% of SECTRAL patients: Cardiovascular: hypotension, bradycardia, heart failure. CNS:

anxiety, hyper/hypoesthesia. impotence. Skin: pruritus. Gastrointestinal: vomiting. abdominal pain. Genitourinary. dysuria. nocturia. Liver and Biliary: small number of addominal pain. Gerindumary, dysaida. Noctain. Poter are binary, and internet reported cases of liver abnormalities (increased SGOT, SGPT, LDH). In some cases, increased bilirubin or alkaline phosphatase, fever, malaise, dark urine, anorexia, nausea, headache, and/or other symptoms have been reported. In some cases, symptoms and signs were contirmed by rechallenge. Abnormalities were reversible upon drug cessation. Musculoskeletal: back and joint pain. Respiratory: pharyngitis wheezing. Special Senses: conjunctivitis, dry eye, eye pain. Autoimmune: extremely

rare reports of systemic lupus erythematosis.

Incidence of drug-related adverse effects (volunteered and solicited) based on SECTRAL dose is shown below. (Data from 266 hypertensive patients treated for 3 months on a constant dose.)

Body System	400 mg/day (N = 132)	800 mg/day (N = 63)	1200 mg/day (N = 71)
Cardiovascular	5%	2%	1%
Gastrointestinal	3%	3%	7%
Musculoskeletal	2%	3%	4%
Central Nervous System	9%	13%	17%
Respiratory	1%	5%	6%
Skin	1%	2%	1%
Special Senses	2%	2%	6%
Genitourinary	2%	3%	1%

Potential Adverse Effects: Certain adverse effects not listed above have been reported with other β-blocking agents and should be considered as potential advereffects of SECTRAL

CNS: Reversible mental depression progressing to catatonia, an acute syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see CONTRAINDICATIONS) Allergic: Erythematous rash, fever with aching and sore throat, laryngospasm, respiratory distress.

Hematologic: Agranulocytosis, nonthrombocytopenic and thrombocytopenic purpt. Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Misc.: Reversible alopecia, Peyronie's disease. The oculomucocutaneous syndromic associated with practolol has not been reported with SECTRAL.

Keep at room temperature. Approximately 25°C (77°F).

3482-5 6/21/89



MISCELLANEOUS

Risk of Cardiovascular Mortality in Alcohol Drinkers, Ex-**Drinkers and Nondrinkers**

Arthur L. Klatsky, Mary Anne Armstrong, and Gary D. Friedman

This new prospective study of 1,002 cardiovascular deaths among 123,840 persons showed that ex-drinkers and infrequent drinkers had similar cardiovascular mortality to that of lifelong abstainers. Use of more alcohol was associated with a higher mortality risk from hypertension, cardiomyopathy and hemorrhagic stroke but with a lower mortality risk from coronary artery disease (CAD), occlusive stroke and nonspecific cardiovascular syndromes. The CAD subset (n = 600) dominated the cardiovascular statistics, which showed an overall U-shaped alcohol mortality relation (nadir at 1 to 2 drinks/day). The relation of alcohol to CAD mortality was independent of baseline risk or reasons for quitting. These data show that the higher cardiovascular mortality rate of abstainers, compared to lighter drinkers, is not due to former drinking or to baseline risk. The findings indirectly support a protective effect of alcohol against CAD.

1243

Subnormal Parasympathetic Activity After Cardiac **Transplantation**

Michael L. Smith, Kenneth A. Ellenbogen, Dwain L. Eckberg, Helen M. Sheehan, and Marc D. Thames

Heart period variability was measured during quiet rest in 18 patients with heart failure before and twice after orthotopic cardiac transplantation and in 16 age-matched control subjects. Heart period variability of innervated recipient atria did not change significantly from pretransplantation to early (1 to 4 weeks) posttransplantation, but did increase significantly (change = 14 ± 3 ms; p = 0.002) after late posttransplantation (15 to 37 weeks). A regression model showed that heart period variability of innervated recipient atria was related directly to time after transplantation and inversely to systolic pressure after transplantation and degree of rejection. Heart period variability of the denervated donor atria remained unchanged after transplantation.

1247

Natural History of Cardiac Rhabdomyoma in Infancy and Childhood

John F. Smythe, John D. Dyck, Jeffrey F. Smallhorn, and Robert M. Freedom

Although spontaneous regression of cardiac rhabdomyoma has been reported, prognosis is still considered to be poor and surgery continues to be indicated. Experience with rhabdomyoma in infancy over a 20-year period was reviewed. Diagnosis by angiography or echocardiography was accepted only if multiple tumors were present or if tuberous sclerosis was also diagnosed. Nine patients were identified as having a total of 24 tumors. All had at least some evidence of regression, with 20 of 24 showing complete resolution. Results suggest that pediatric cardiac rhabdomyoma is most

Continued on page A40



Images are actual printout size.

For more detail, pl

On the left, we have a printout from a leading video printer. On the right, a printout from Mitsubishi's new P-40U.

Notice the fine detail in the printout on the right. It amounts to a big improvement in picture quality.*

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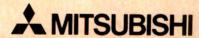
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ty vary according to subject matter.

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often a benign condition in which spontaneous regression is the rule. Surgery is recommended only for patients with refractory dysrhythmias or severe hemodynamic compromise.

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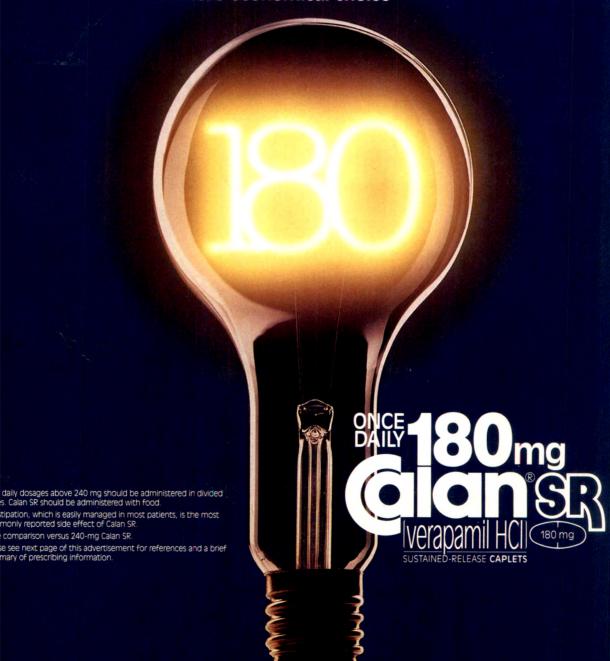
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A BRIGHT IDEA... IN MILD TO MODERATE HYPERTENSION

180-mg Calan SR...once-daily, single-agent therapy

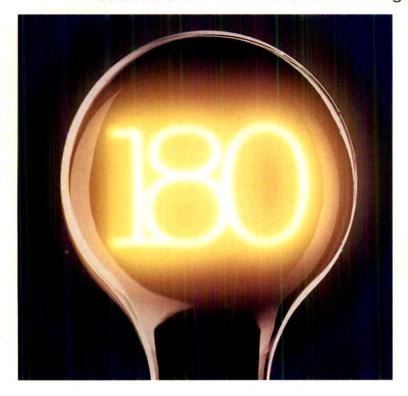
- Efficacy proven comparable to 240 mg¹
- 24-hour control with once-daily dosing¹*
- Low-dose, well-tolerated therapy

A more economical choice[‡]



Consistent with 1988 JNC recommendation...

The 1988 report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure recommends that blood pressure be controlled "...with the fewest drugs at their lowest dose..."²



When you want high single-agent efficacy in a lower dose, prescribe...



A BRIGHT IDEA in verapamil SR therapy

References:

 Data on file, G.D. Searle & Co. 2. 1988 Joint National Committee The 1988 report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. Arch Intern Med 1988;148:1023-1038.

BRIEF SUMMARY

Contraindications: Severe LV dysfunction (see *Warnings*), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), hypersensitivity to verapamil.

Warnings: Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction < 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported. Several cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation, and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (2nd- and 3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive begative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol clearance may occur with combined use. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration.

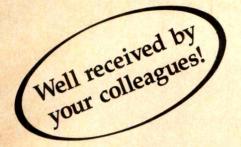
Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with ypertrophic cardiomyopathy should be avoided, since significant hypotension may result Concomitant use of lithium and verapamil may result in a lowering of serum lithium levels of increased sensitivity to lithium. Patients receiving both drugs must be monitored carefully Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduct verapamil bloavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporin. Concomitant use of inhalation anesthetics and calcium antagonist needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiat the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. Adequate animal carcinogenicity studies have not been performed. One studin rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ame test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnar women. This drug should be used during pregnancy, labor, and delivery only if clearly needer Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamils.

Adverse Reactions: Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (2.5% headache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4% bradycardia: HR < 50/min (1.4%), AV block: total 1°,2°,3° (1.2%), 2° and 3° (0.8%), ras (1.2%), flushing (0.6%), elevated liver enzymes. The following reactions, reported in 1.0% cless of patients, occurred under conditions where a causal relationship is uncertain: angin pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitation purprura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasis ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnic muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, arthralgia and rast exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome erythema multiforme, blurred vision, gynecomastia, increased urination, spotty menstruatior impotence.

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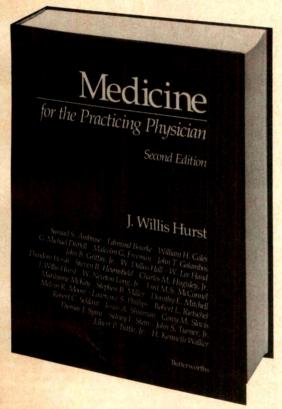
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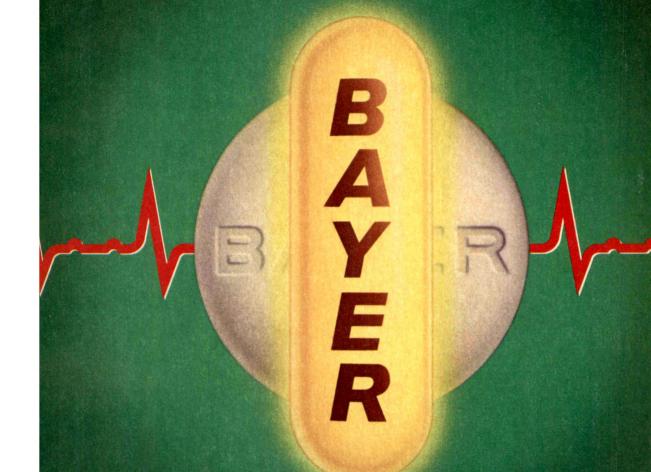
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Brief Summary

Therapy BAYER® Aspirin

Delayed-Release Enteric Aspirin (Acetylsalicylic Acid) Caplets to Help Reduce the Risk of Second MI or MI in Unstable Angina

DOSAGE AND ADMINISTRATION:

Although most of the studies used dosages exceeding 300 mg, two trials used only 300 mg daily, and pharmacologic data indicate that this dose inhibits platelet function fully. Therefore, 300 mg or a conventional 325 mg aspirin dose daily is a reasonable routine dose that would minimize gastrointestinal adverse reactions. This use of aspirin applies to both solid oral dosage forms (buffered and plain aspirin) and buffered aspirin in solution.

CARDIOVASCULAR AND BIOCHEMICAL:

In the AMIS trial, the dosage of 1,000 mg per day of aspirin was associated with small increases in systolic blood pressure (BP) (average 1.5 to 2.1 mm) and diastolic BP (0.5 to 0.6 mm), depending upon whether maximal or last available readings were used. Blood urea nitrogen and uric acid levels were also increased but by less than 1.0 mg percent. Subjects with marked hypertension or renal insufficiency had been excluded from the trial so that the clinical importance of these observations for such subjects or for any subjects treated over more prolonged periods is not known. It is recommended that patients placed on long-term aspirin treatment, even at doses of 300 mg per day, be seen at regular intervals to assess changes in these measurements.

BIOAVAILABILITY:

The bioavailability of aspirin from Therapy BAYER has been confirmed. In a single-dose study¹ in which plasma acetylsalicylic acidiand salicylic acid levels were measured, measurable plasma concentrations were achieved within 15 minutes after dosing. Maximum concentrations were achieved at approximately five hours postdosing. Therapy BAYER, when compared with plain aspirin, achieves maximum plasma salicylate levels not significantly different from plain, i.e., not enteric-coated, aspirin. Dissolution of the enteric coating occurs at a neutral-to-basic pH and is therefore dependent on gastric emptying into the duodenum. With continued dosing, appropriate therapeutic plasma levels are maintained.

SAFFTY-

The safety of enteric-coated aspirin has been demonstrated in a number of endoscopic studies comparing enteric-coated aspirin and plain aspirin, as well as plain buffered and "arthritis strength" preparations. In these studies, endoscopies were performed in healthy volunteers before and after either two-day or 14-day administration of aspirin doses of 3,900 or 4,000 mg/day. Compared to all the other preparations, the enteric-coated aspirin produced significantly less damage to the gastric mucosa. There was also statistically less duodenal damage when compared with the plain, i.e., non-enteric-coated, aspirin.

ADVERSE REACTIONS:

Gastrointestinal reactions: Doses of 1,000 mg per day of aspirin caused gastrointestinal symptoms and bleeding that, in some cases, were clinically significant. In the largest postinfarction study (the Aspirin Myocardial Infarction Study [AMIS] with 4,500 people),² the percentage of incidences of gastrointestinal symptoms for the aspirin (1,000 mg of a standard, solid-tablet formulation) and placebo-treated subjects, respectively, were stomach pain (14.5%, 4.4%), heartburn (11.9%, 4.8%), nausea and/or vomiting (7.6%, 2.1%), and hospitalization for GI disorder (4.9%, 3.5%). In the AMIS and other trials, aspirin-treated patients had increased rates of gross gastrointestinal bleeding. Symptoms and signs of gastrointestinal irritation were not significantly increased in subjects treated for unstable anging with buffered aspirin in solution.

PROFESSIONAL WARNING:

Occasional reports have documented individuals with impaired gastric emptying in whom there may be retention of one or more enteric-coated aspirin caplets over time. This phenomenon may occur as a result of outlet obstruction from ulcer disease alone or combined with hypotonic gastric peristalsis. Because of the integrity of the enteric coating in an acidic environment, these caplets may accumulate and form a bezoar in the stomach. Individuals with this condition may present with complaints of early satiety or of vague upper abdominal distress. Diagnosis may be made by endoscopy or by abdominal films, which show opacities suggestive of a mass of small caplets. Management may vary according to the condition of the patient. Options include gastrotomy and alternating slightly basic and neutral lavage. While there have been no clinical reports, it has been suggested that such individuals may also be treated with parenteral cimetidine (to reduce acid secretion) and then given sips of slightly basic liquids to effect gradual dissolution of the enteric coating. Progress may be followed with plasma salicylate levels or via recognition of tinnitus by the patient.

It should be kept in mind that individuals with a history of partial or complete gastrectomy may produce reduced amounts of acid and therefore have less acidic gastric pH. Under these circumstances, the benefits offered by the acid-resistant enteric coating may not exist.

REFERENCES:

1. Data on file, Glenbrook Laboratories. 2. Aspirin Myocardial Infarction Study Research Group: A randomized, controlled trial of aspirin in persons recovered from myocardial infarction. *JAMA* 1980;245:661-669. 3. Bogacz K, Caldron P: Enteric-coated aspirin bezoar: Elevation of serum salicylate level by barium study. *Am J Med* 1987;83:783-786. 4. Baum J: Enteric-coated aspirin and the problem of gastric retention. *J Rheumatol* 1984;11:250-251.



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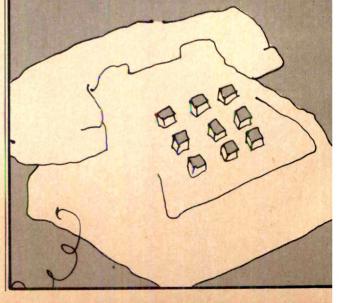
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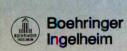
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Exercise Test Predictors of Ambulatory Silent Ischemia During Daily Life in Stable Angina Pectoris

Prakash C. Deedwania, MD, and Enrique V. Carbajal, MD, with the technical assistance of Kippur Spears

The predictive value of several exercise test parameters in identifying stable angina patients at risk of silent myocardial ischemia during daily life were examined. A total of 97 patients with coronary artery disease, stable angina and ambulatory electrocardiographic data were evaluated. Of the 86 patients with a positive exercise test, 39 (group 1) had ≥1 episodes of ST-segment depression and 47 (group 2) did not develop ST changes during ambulatory electrocardiographic monitoring. Comparison of the exercise test parameters between the 2 groups revealed early onset of ischemia during exercise tests as the single most significant (p <0.0005) predictor of ambulatory silent ischemia. The other exercise test parameters showing significant differences between the 2 groups were the peak exercise heart rate (117 \pm 23 vs 126 \pm 20 beats/min, p <0.05) and peak systolic blood pressure (160 \pm 27 vs 176 \pm 27 mm Hg, p <0.01), both of which were significantly lower in the group 1 patients. These data were used to derive simple mathematical formulas for calculating the risk of ambulatory silent ischemia. These results demonstrate that stable angina patients at risk of silent ischemia during daily life can be accurately identified by evaluation of selected exercise test parame-

(Am J Cardiol 1990;66:1151-1156)

Recent studies of patients with stable coronary artery disease have demonstrated that silent myocardial ischemia during daily life is an indicator of adverse clinical outcome and poor survival. Although exercise test findings correlate well with subsequent risk of cardiac events, it has been suggested that in patients with stable coronary artery disease and a positive exercise test, prolonged cumulative ischemia on ambulatory electrocardiographic monitoring identifies a subset of patients with extensive coronary artery disease and adverse prognoses. 1-4 These findings have generated considerable interest and enthusiasm for monitoring ambulatory ST-segment changes in patients with stable coronary artery disease.

Recent technologic advances have led to the development of several reliable ambulatory electrocardiographic monitoring systems for the detection of silent ischemia during daily life; however, these systems are not readily available and routine ambulatory electrocardiographic monitoring in patients with stable angina would increase the cost of health care considerably. Although some series have reported silent ischemia in 40 to 50% of patients with stable angina, 1,2 a recent report suggested a lower prevalence.3 Thus, routine ambulatory monitoring for ST-segment changes seems impractical and may be unnecessary in a majority of patients with stable angina. However, it would be clinically useful if patients at risk of silent ischemia during daily life could be identified based on results of exercise testing, which is performed routinely in these patients. In this prospective study we evaluated the predictive value of several commonly used exercise test parameters in identifying those patients with stable exertional angina who are at risk of developing silent ischemia during daily life.

METHODS

Patients: Consecutive male patients (n = 97) with clinical evidence of coronary artery disease and stable angina were enrolled from the medicine and cardiology clinics between October 1985 and July 1987. All patients gave informed consent for participation in the study, which was approved by the hospital's human study and research committees. All patients had classic exertional angina for ≥ 6 months. The diagnosis of coronary artery disease was confirmed by ≥ 1 of the following: significant ($\geq 70\%$) luminal diameter narrowing of

From the Department of Medicine, Division of Cardiology, Department of Veterans Affairs Medical Center, Fresno, California and the University of California School of Medicine, San Francisco, California. Manuscript received March 23, 1990; revised manuscript received and accepted July 9, 1990.

Address for reprints: Prakash C. Deedwania, MD, Division of Cardiology, Department of Medicine, University of California at San Francisco Program/Veterans Affairs Medical Center, 2615 East Clinton Avenue, Fresno, California 93703.

TABLE I Comparison of Baseline Clinical Characteristics of Patients With (Group 1) and Without (Group 2) Silent Ischemia During Ambulatory Electrocardiographic Monitoring

	Group 1 (n = 39)	Group 2 (n = 47)	p Value
Mean age (yrs)	64±8	63±6	NS
Angina duration (mos)	103 ± 76	112 ± 82	NS
Previous myocardial infarction (%)	18 (46)	23 (49)	NS
Systemic hypertension (%)	25 (64)	31 (66)	NS
Cigarette smoking (%)	25 (64)	33 (70)	NS
Diabetes mellitus (%)	10 (26)	12 (26)	NS
Total cholesterol (mg/dl)	245 ± 105	228 ± 44	NS
O waves (%)	17 (44)	18 (38)	NS

≥1 major coronary arteries, reversible myocardial perfusion defect on exercise thallium-201 scintigraphy, or a well-documented myocardial infarction. Patients were excluded if they had conditions that affected the evaluation of ST depression on the electrocardiogram, such as severe left ventricular hypertrophy, left bundle branch block, preexcitation syndromes, pacemaker rhythms and uncorrected hypokalemia. Those receiving digitalis or tricyclic antidepressants were also excluded. All patients continued taking antianginal drug therapy at stable doses as prescribed by their primary physicians.

Study design: Maximal treadmill testing was performed by a trained physician. The leads showing the greatest ST depression during exercise were selected for ambulatory electrocardiographic monitoring. Holter tapes were coded to mask the patients' identities. The majority of patients had the exercise and ambulatory monitoring tests performed within a 6-month period. The results of ambulatory electrocardiographic recordings and the exercise treadmill tests were analyzed independently at a later date in a blinded fashion.

Ambulatory electrocardiographic monitoring: Continuous 24-hour 2-channel ambulatory electrocardiographic recordings were obtained with validated and calibrated frequency modulated tape recorders (Oxford Medilog MR 20) with a frequency-response range between 0.05 and 100 Hz, which meets the American

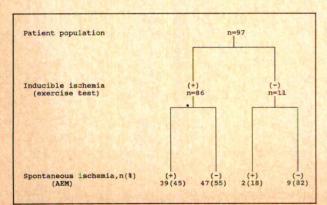


FIGURE 1. Classification of the study group and findings during exercise testing and ambulatory electrocardiographic monitoring. AEM = ambulatory electrocardiographic monitoring.

TABLE II Comparison of Baseline Angiographic Data of Patients With (Group 1) and Without (Group 2) Silent Ischemia Detected by Ambulatory Electrocardiographic Monitoring

	Group 1	Group 2	p Value
Thallium-201 scintigraphy with reversible defect	27	31	
Mean score ± SD Angiogram*	15 ± 27	10 ± 21	NS
No. of coronary arteries >70% in diameter	29	33	
1 (%)	4(14)	6(18)	NS
2(%)	9(31)	15 (45)	NS
3(%)	16 (55)	12 (36)	NS
Left main artery	4(14)	7 (21)	NS
No. with LVEF data	28	42	
Mean % LVEF	49 ± 11	53 ± 11	NS

* Angiographic findings showing >70% luminal narrowing. LVEF = left ventricular ejection fraction; NS = not significant; SD = standard

Heart Association standards for evaluation of the ST segment.⁵ A left precordial and an inferior or anterior lead corresponding to the location of maximum ST depression during the exercise test were selected. The electrocardiograph leads with Q waves or baseline ST depression were avoided. Baseline electrocardiographic recordings were obtained for each patient before and after hyperventilation, and in the supine, prone, sitting and standing positions to ensure that the ST segment was not affected by these postural changes. Patients were instructed to press an event button on the recorder if they experienced an episode of angina during their usual activities and to record the number and duration of episodes. The tapes were scanned at 60 to 120 times real time on a playback analyzer unit (Oxford Medilog MA 20) by an experienced technician for the presence, frequency and duration of ischemic ST depression. An ischemic episode was defined as ≥1 mm horizontal or downsloping ST depression, 80 ms from the J point, and lasting ≥1 minute. An interval of ≥2 minutes, during which the ST segment returned to the baseline level, was required before another discrete episode was count-

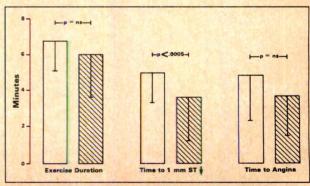


FIGURE 2. Comparison of exercise duration, exercise time to ischemia, and exercise time to angina between patients with (hatched bars) and patients without (open bars) silent ischemia during ambulatory electrocardiographic monitoring. NS = not significant.

ed. The technician scanning the tapes identified all ischemic episodes meeting these criteria and recorded the time of onset, peak ST depression and termination of the events. Electrocardiographic tracings of these episodes were obtained at a speed of 25 mm/s for review. Hourly examples of baseline measurements without ST changes were also recorded on paper. For each patient, the total number of episodes and the total duration of episodes in minutes were determined every 24 hours. All episodes of ST depression were identified as being either symptomatic or silent based on the details of angina diaries. The ambulatory electrocardiographic recordings were blindly and independently reviewed by ≥2 experienced investigators, who performed visual and real-time printout analyses of the monitoring periods showing ST depression. In case of a discrepancy between the 2 observers, the tapes were reanalyzed. Only those tapes with interpretable signals for ≥18 hours per recording period were included in the final analysis.

Exercise testing: All patients underwent multistage symptom-limited exercise treadmill testing using the Bruce protocol. A positive exercise ischemic response was defined as ≥1 mm horizontal or downsloping ST depression measured 80 ms after the J point. The test was terminated at the point of physical exhaustion, severe angina, ST depression >2 mm, hypotension >20 mm Hg, complex ventricular arrhythmia, severe dyspnea, or claudication. The total exercise time, time to onset of ischemia, time to angina, heart rate and blood pressure at rest, at the onset of 1-mm ST depression and peak exercise and maximal ST depression during exercise were recorded.

Statistical analysis: Based on the results of previous studies, several exercise test parameters were evaluated and compared between the 2 groups using the group t test of significance. Subsequently, the relation between selected exercise test parameters and ambulatory electrocardiographic monitoring findings were evaluated by linear regression analysis. The clinical variables for the

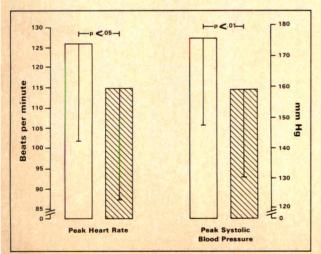


FIGURE 3. Comparison of peak heart rate and peak systolic blood pressure during exercise between patients with (hatched bars) and patients without (open bars) silent ischemia during ambulatory electrocardiographic monitoring.

2 groups were compared using unpaired t test of significance for continuous variables, and chi-square analysis was performed for categorical variables. Data are expressed as frequency or mean (\pm standard deviation) for normally distributed and continuous variables, respectively; otherwise, they are reported as the median and range. Statistical significance is defined by a p value ≤ 0.05 .

Classification of patients at risk of ambulatory silent ischemia: The exercise test data were analyzed by 2 separate methods to derive simple mathematic formulas to calculate the risk of ambulatory silent ischemia. The first method used a pattern classification system,6 and the second used a binary decision tree. The pattern classification system used a supervised learning approach, in which data of known classification were used to establish weights for each parameter contributing to the decision. The magnitude of each weight indicated the degree to which that parameter contributed to the final outcome for detection of ambulatory silent ischemia. This resulted in a simple algebraic expression, which yields a numerical value when data for each case are entered. A negative value identifies patients at risk, whereas a positive value identifies those not at such risk. The numerical magnitude also correlates with the degree of certainty regarding the accuracy of the classification.

The second method used a binary decision tree, which the evaluator follows in order to classify the patients with and without risk of ambulatory silent ischemia. In a stepwise manner, the top node of the tree initially asked if a given variable was < or > an assigned value. If it was > the assigned value, the evaluator proceeded down the tree to the right; if it was < the assigned value, the evaluator proceeded down to the left. The final destination was a terminal node, which classified the patients into groups with and without ambulatory silent ischemia.

RESULTS

Clinical characteristics: The mean age of the group (n = 97) was 63 ± 7 years, with an average duration of angina of 107 ± 79 months. There were 86 patients with and 11 without inducible ischemia during exercise testing (Figure 1). Ambulatory electrocardiographic

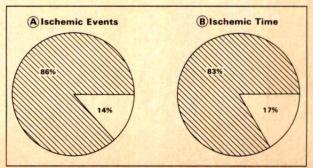


FIGURE 4. Pie charts showing the proportion of silent (hatched areas) and symptomatic (open areas) ischemic events (A) and total ischemic time (B) during ambulatory electrocardiographic monitoring.

monitoring revealed ≥1 transient ischemic event in 45% of patients with compared to only 18% (2 of 11) of patients without a positive exercise test. To compare the predictive value of exercise parameters in identifying patients at risk of silent ischemia during daily life, the 86 patients with a positive exercise test and ambulatory monitoring data were divided into 2 groups: patients with (group 1, n = 39) and without (group 2, n = 47) transient ischemia during ambulatory electrocardiographic monitoring. Comparison of baseline clinical characteristics (Table I) and angiographic findings (Table II) revealed no significant difference between the groups.

Exercise test parameters: Although the total exercise time did not differ significantly between the groups (Figure 2), the time to ischemia during exercise was significantly shorter $(3.7 \pm 1.8 \text{ vs } 5.0 \pm 1.7 \text{ minutes}, \text{ p})$ <0.0005) in patients with ambulatory silent ischemia. Comparison of patients with exercise-induced silent ischemia did not reveal a significant difference between the 2 groups (38 and 43% in groups 1 and 2, respectively) and absence of exertional angina did not predict risk of ambulatory silent ischemia. Analysis of hemodynamic parameters during exercise revealed significant differences between the groups (Figure 3). The peak heart rate (117 \pm 23 vs 126 \pm 20 beats/min, p <0.05) and peak systolic blood pressure (160 \pm 27 vs 176 \pm 27 mm Hg, p <0.01) during exercise were significantly lower in patients with ambulatory silent ischemia.

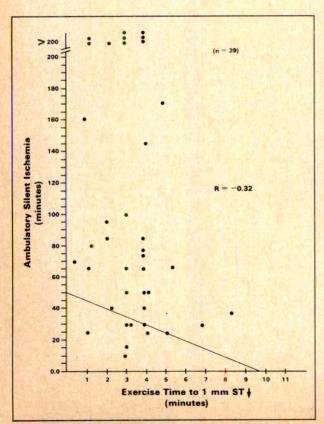


FIGURE 5. Linear regression analysis plot of ambulatory silent ischemia duration versus exercise time to onset of ischemia. An inverse correlation (r=-0.32, p=0.004) that is significant but weak is demonstrated.

Ambulatory electrocardiographic findings: During 2,064 hours of ambulatory electrocardiographic monitoring, there were 154 transient ischemic events. Approximately 86% of these ischemic events were silent and accounted for the majority of the total (5,500 minutes) ischemic time (Figure 4). The average number and duration of ischemic events during the 24-hour monitoring period was 3.4 ± 3 and 117 ± 115 minutes (median 70; range 8 to 468), respectively. There were 29 (74%) patients with silent ischemic events only, and 10 had both silent and symptomatic events during ambulatory electrocardiographic monitoring. Although the duration of symptomatic events (55 \pm 63 minutes) was longer than silent events (27 \pm 18), this was not statistically significant.

Exercise test predictors of ambulatory silent ischemia: Several exercise test parameters were tested for their ability in identifying patients at risk of ambulatory silent ischemia. The number and duration of silent ischemic events during ambulatory electrocardiographic monitoring were correlated with selected exercise test variables by linear regression analyses. There was no relation between the ambulatory monitoring findings and the total exercise duration or exercise time to angina. Although patients with ambulatory silent ischemia had significantly lower peak heart rate and systolic blood pressure during exercise, these parameters also did not show any correlation with Holter monitoring findings. In contrast, the time to onset of exercise-induced ischemia showed a significant relation with Holter findings. Figure 5 shows a significant (p < 0.005) although weak inverse relation (r = -0.32) between the duration of ambulatory silent ischemia and time to onset of ischemia during exercise testing. Of 39 patients with silent ischemia during daily life, 37 (95%) developed ischemia within the first 6 minutes of exercise testing (95% confidence intervals, 81 to 99%).

Prediction of ambulatory silent ischemia by mathematic models: Both mathematic models provided clinically useful predictive formulas for identification of patients at risk of silent ischemia during daily life. The first method, using a pattern classification system (Figure 6), produced the following algebraic expression: De-

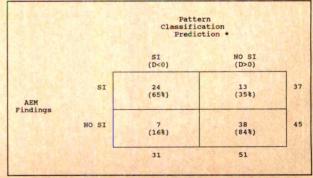


FIGURE 6. Results of analysis by pattern classification method in predicting risk of ambulatory silent ischemia (SI) using the formula D=(6t+37d/10,000)-92, where t=time to onset of ischemia (minutes) and d=peak double product. The derived score D of <0 indicates risk of silent ischemia during ambulatory electrocardiographic monitoring (AEM).

rived score (D) = (6t + 37d/10,000) - 92, where t = time to onset of exertional ischemia and d = peak exercise double product; if D was <0 it indicated risk of ambulatory ischemia, and if >0 it suggested no risk. The sensitivity, specificity and predictive accuracy by this method were 65, 84, and 76%, respectively.

The results of the second method, using the binary decision tree, are shown in Figure 7. Of the 82 patients with a positive exercise test, 54 developed ischemia within 4.25 minutes of exercise and were initially classified as those at risk of ambulatory silent ischemia. They were further substratified based on a peak exercise double product of ≤20,000 or more. Of these 54, 28 had a peak exercise double product ≤20,000, and 23 (82%) of these 28 had ambulatory silent ischemia. In contrast, only 2 (11%) of the 18 patients with delayed onset of ischemia (>4.25 minutes) and a higher (>20,000) peak exercise double product had silent ischemia during ambulatory monitoring. The overall sensitivity, specificity and predictive accuracy of this method were 62, 89 and 77%, respectively (Figure 8).

DISCUSSION

These findings demonstrate that selected exercise test parameters can accurately identify stable angina patients who are at risk of ambulatory silent ischemia during daily life.

Although we only had a small number of patients with a negative exercise test (2 of 11), our data in such patients are consistent with the results of several recent studies in showing that stable angina patients with a negative exercise test rarely develop silent ischemia during ambulatory monitoring.7-10 In the most recent study of 277 patients with coronary artery disease, Mulcahy et al⁹ found that >90% of ischemic episodes on ambulatory monitoring occurred in patients with a positive exercise test. These findings are of clinical importance and show that ambulatory ST-segment monitoring is of little clinical benefit in patients with a negative exercise test. Most previous reports, however, failed to address the issue of risk stratification for ambulatory silent ischemia in the vast majority of patients with coronary artery disease who have a positive exercise test.

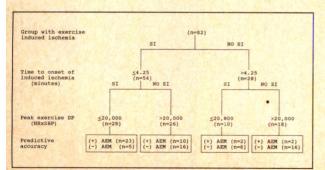


FIGURE 7. Stratification of 82 patients by the binary decision tree method. The top node of the tree stratifies patients based on time to onset of ischemia during exercise testing and the subsequent classification is based on peak exercise double product ≤20,000 or more. The terminal node shows the final results based on ambulatory electrocardiographic monitoring (AEM) findings. DP = double product; HR = heart rate; SBP = systolic blood pressure; SI = silent ischemia.

It is known that in patients with stable coronary artery disease and exercise-induced ischemia, most (70 to 80%) transient ischemic episodes are not associated with symptoms. 1,2,11-14 Because the presence of ambulatory silent ischemia is associated with adverse clinical outcome and poor survival, 1,2 ambulatory ST-segment monitoring is gaining popularity in the clinical evaluation of patients with coronary artery disease. However, the technologic requirements, lack of availability of appropriate equipment and the associated high cost make routine ambulatory electrocardiographic monitoring impractical. Although the exact prevalence is not known, it is estimated, based on available data, that between 37 and 50% of stable angina patients with a positive exercise test are at risk of silent ischemia during daily life. 1-3 Thus, it would be useful if such patients could be identified by the evaluation of clinical characteristics and data obtained during routine exercise treadmill testing.

Our findings show that most patients with a positive exercise test who are at risk of silent ischemia during daily life can be accurately identified by evaluation of selected exercise test parameters obtained during routine testing. The most important parameter was the time to onset of exercise-induced ischemia. Of the 39 patients with ≥1 episodes of transient ischemia during ambulatory monitoring, 37 (95%) developed ischemia within the first 6 minutes of exercise testing and thus could be identified by using this simple exercise test parameter. These findings are similar to those of a previous report in a smaller group of patients.8 In that study, the relation between exercise-induced ischemia and the out-of-hospital ischemic activity was evaluated in 39 patients with documented coronary artery disease and revealed earlier onset of ST-segment depression during exercise testing as the most significant predictor of outof-hospital ischemic activity.

Although time to onset of exercise-induced ischemia is a predictor of ambulatory silent ischemia, a controversy remains regarding its relation with the duration of ischemia during ambulatory monitoring.^{3,8} In contrast to these previous observations, the linear regression analysis in our study revealed an inverse relation between the time to onset of ischemia during exercise and the duration of silent ischemia during ambulatory electrocardiographic monitoring (Figure 5). Although statistically significant, this relation is weak (r = -0.32) and may be related to the fact that ischemia during dai-

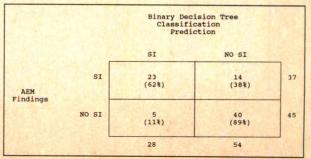


FIGURE 8. Results of analysis by binary tree classification method in predicting risk of ambulatory silent ischemia. Abbreviations as in Figure 7.

ly life occurs due to mechanisms other than those responsible for exercise-induced ischemia. The results of a previous report¹¹ demonstrated that many episodes of silent ischemia during daily life occur without a significant increase in the heart rate and may be secondary to a primary decrease in coronary blood flow.

Predictive model for ambulatory silent ischemia: The pattern recognition analysis and the binary decision tree model are simple methods that can be used in the routine clinical setting to evaluate the risk of ambulatory silent ischemia on a case-by-case basis. By using the simple calculation—the time to onset of exercise-induced ischemia and peak double product—these formulas provide reliable means of predicting the risk of silent ischemia during daily life. In the pattern classification system, a simple formula can be used: D = (6t + 37d)10,000) - 92, where t = time to onset of ischemia (minutes) and d = peak double product. If the derived score D is <0, it indicates risk of silent ischemia during daily life.

In the binary decision tree model, a simple evaluation using the time to onset of exercise-induced ischemia of ≤4.25 minutes initially identifies most patients at risk of ambulatory silent ischemia. Further stratification by using the peak double product of ≤20,000 identified the group (80% of patients) at greatest risk of silent ischemia during daily life.

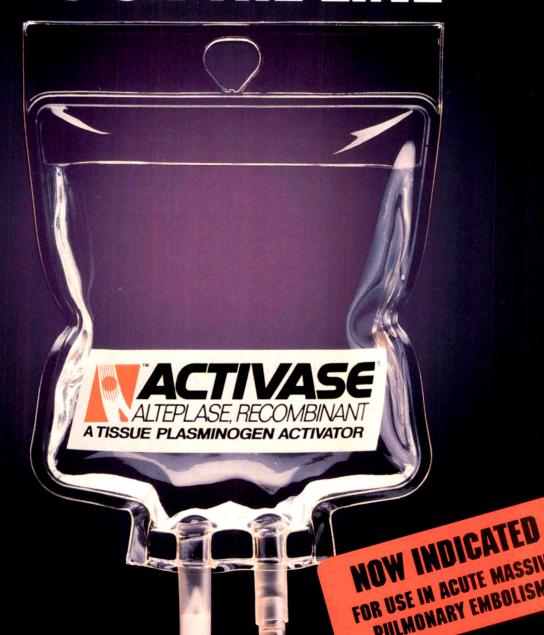
Conclusions: Our results provide clinically relevant information by showing that selected exercise test parameters obtained during routine testing can accurately predict the risk of silent ischemia during daily life. Although it is generally believed that most patients with stable coronary artery disease and a positive exercise test are at increased risk of silent ischemia during daily life, our data show that simple evaluation using the time to onset of ischemia and the peak double product obtained during a routine exercise test can accurately identify patients at greatest risk. The 2 simple formulas provided for calculating the risk of ambulatory silent ischemia should be useful in determining the need of ambulatory electrocardiographic monitoring for patients who may be at increased risk of future cardiac events because of the presence of silent ischemia during daily life.

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Brief Summary
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INDICATIONS AND USAGE: ACTIVASE® is indicated for use in the management of acute myocardial infarction (AMI) in adults for the lysis of thrombi obstructing coronary arteries, the reduction of infarct size, the improvement of ventricular function following AMI, the reduction of the incidence of congestive heart failure and the reduction of mortality associated with AMI. Treatment should be initiated as

on as possible after the onset of AMI symptoms.

TIVASE® is also indicated in the management of acute massive pulmonary embolism (PE) in adults: for the lysis of acute pulmonary emboli, defined as obstruction of blood flow to a been or multiple segments of the lungs, and for the lysis of pulmonary emboli accompanied by unstable hemodynamics, i.e., failure to maintain blood pressure without supportive measures. The diagnosis should be confirmed by objective means, such as pulmonary angiography or noninvasive procedures such

as lung scanning.

CONTRAINDICATIONS: Because thrombolytic therapy increases the risk of bleeding, ACTIVASE* is contraindicated in the following situations: Active internal bleeding - History of carebrovascular accident - Recent (within two months) intracranial or intraspinal surgery or trauma (see WARNINGS) - Intracranial neoplasm, arteriovenous malformation, or aneurysm - Known bleeding diathesis - Severe uncontrolled hypertension.

WARNINGS: Bleeding The most common complication encountered during ACTIVASE* therapy beleeding. The type of bleeding associated with thrombolytic therapy can be divided into two broad categories: -Internal bleeding involving the gastrointestinal or genitourinary tract, or retroperitoneal or intracranial sites - Superficial or surface bleeding, observed mainly at invaded or disturbed sites (e.g., sites of venous cutdown, arterial puncture, recent surgical intervention).

Concomitant use of heparin anticoagulation may contribute to bleeding. Some hemorrhagic episodes occurred one or more days after the effects of ACTIVASE* had dissipated, but while heparin therapy was continuing.

was continuing

occurred one or more days after the effects of ACTIVASE® had dissipated, but while heparin therapy was continuing.

As fibrin is lysed during ACTIVASE® therapy, bleeding from recent puncture sites may occur. Therefore, thrombolytic therapy requires careful attention to all potential bleeding sites (including sites of catheter insertion, arterial and venous puncture, cutdown and needle puncture). Intramuscular injections and nonessential handling of the patient should be avoided during treatment with ACTIVASE® Venipunctures should be performed carefully and only as required. Should an arterial puncture be necessary during an infusion of ACTIVASE® it is preferable to use an upper extremity vessel accessible to manual compression. Pressure should be applied for at least 30 minutes, a pressure dressing applied and the puncture site checked frequently for evidence of bleeding. Should serious bleeding (not controllable by local pressure) occur, the infusion of ACTIVASE® and any concomitant heparin should be terminated immediately.

Each patient being considered for therapy with ACTIVASE® should be carefully evaluated and anticipated benefits recent (within 10 days) major surgery, e.g., coronary artery bypass graft, obstetrical delivery, organ biopsy, previous puncture of noncompressible vessels • Cerebrovascular disease • Recent (within 10 days) major surgery, e.g., coronary artery bypass graft, obstetrical delivery, organ biopsy, previous puncture of noncompressible vessels • Cerebrovascular disease • Recent (within 10 days) gastrointestinal or genitourinary bleeding • Recent (within 10 days) grain and the particular handle provided the provided provide

deep venus thrombis should be considered.

PRECAUTIONS: General Standard management of myocardial infarction or pulmonary embolism should be implemented concomitantly with ACTIVASE® treatment. Noncompressible arterial puncture must be avoided. Arterial and venous punctures should be minimized. In the event of serious bleeding, ACTIVASE® and heparin should be discontinued immediately. Heparin effects can be reversed by protamine.

reversed by protamine.

Readministration There is no experience with readministration of ACTIVASE® If anaphylactoid reaction occurs, infusion should be discontinued immediately and appropriate therapy initiated.

Although sustained antibody formation in patients receiving one dose of ACTIVASE® has not been documented, readministration should be undertaken with caution.

Laboratory Tests During ACTIVASE® therapy, results of coagulation tests and/or measures of fibrinolytic activity may be unreliable unless specific precautions are taken to prevent in vitro artifacts.

ACTIVASE® is an enzyme that when present in blood in pharmacologic concentrations remains active under in vitro conditions. This can lead to degradation of fibrinogen in blood samples removed for analysis. Collection of blood samples in the presence of aprotinin (150-200 units/mL) can to some extent mitigate this phenomenon.

extent mitigate this phenomenon.

Drug Interactions The interaction of ACTIVASE® with other cardioactive drugs has not been studied. In addition to bleeding associated with heparin and vitamin K antagonists, drugs that alter platelet function (such as acetylsalicylic acid, dipyridamole) may increase the risk of bleeding if administered prior to, during or after ACTIVASE® therapy.

Use of Anticoagulants Heparin has been administered concomitantly with and following infusions of ACTIVASE* to reduce the risk of rethrombosis. Because either heparin or ACTIVASE* alone may cause bleeding complications, careful monitoring for bleeding is advised, especially at arterial puncture sites. Pregnancy (Category C) Animal reproduction studies have not been conducted with ACTIVASE* it is also not known whether ACTIVASE* can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ACTIVASE* should be given to a pregnant woman only if

clearly needed.

Pediatric Use Safety and effectiveness of ACTIVASE® in children has not been established.

Carcinogenesis, Mutagenesis, Impairment of Fertility Long-term studies in animals have not been performed to evaluate the carcinogenic potential or the effect on fertility. Short-term studies, which evaluated tumorigenicity of ACTIVASE® and effect on tumor metastases in rodents, were negative. Studies to determine mutagenicity (Ames test) and chromosomal aberration assays in human lymphocytes were negative at all concentrations tested. Cytotoxicity, as reflected by a decrease in mitotic index, was evidenced only after prolonged exposure and only at the highest concentrations tested.

Nursing Mothers It is not known whether ACTIVASE® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ACTIVASE® is administered to a nursing woman.

ADVERSE REACTIONS: Bleeding The most frequent adverse reaction associated with ACTIVASE® is bleeding. The type of bleeding associated with thrombolytic therapy can be divided into two broad categories: • Internal bleeding involving the gastrointestinal or genitourinary tract, or retroperitoneal or intracranial sites • Superficial or surface bleeding, observed mainly at invaded or disturbed sites (e.g., sites of venous cutdown, arterial puncture, recent surgical intervention).

The following incidence of significant internal bleeding (estimated as > 250 cc blood loss) has been reported in studies in over 800 patients treated at all doses:

	Total Dose ≤ 100 mg	Total Dose > 100 mg
gastrointestinal	5%	5%
genitourinary	4%	4%
ecchymosis	1%	<1%
retroperitoneal	<1%	<1%
epistaxis	<1%	<1%
gingival	<1%	<1%

The incidence of intracranial bleeding in patients treated with ACTIVASE® Alteplase, recombinant, is as follows:

Dose	Number of Patients	_%_
100 mg 150 mg	3272 1779	0.4
1-1.4 mg/kg	237	0.4

These data indicate that a dose of 150 mg of ACTIVASE® should not be used because it has been

associated with an increase in intracranial bleeding.

Recent data indicate that the incidence of stroke in 6 randomized double-blind placebo controlled trials 17 is not significantly different in the ACTIVASE® treated patients compared to those treated with

placebo (37/3161, 1.2% versus 27/3092, 0.9%, respectively) (p = 0.26).

Should serious bleeding in a critical location (intracranial, gastrointestinal, retroperitoneal, pericardial) occur, ACTIVASE® therapy should be discontinued immediately, along with any concomitant therapy with heparin.

therapy with heparin.

Fibrin, which is part of the hemostatic plug formed at needle puncture sites, will be lysed during ACTIVASE* therapy. Therefore, ACTIVASE* therapy requires careful attention to potential bleeding sites.
Allergic Reactions No serious or life-threatening allergic reactions have been reported. Other mild hypersensitivity reactions such as urticaria have been observed occasionally. Other Adverse Reactions Other adverse reactions have been reported, principally nausea and/or vomiting, hypotension, and fever. These reactions are frequent sequelae of MI and may or may not be attributable to ACTIVASE* therapy.

attributable to ACTIVASE® therapy.

DOSAGE AND ADMINISTRATION: ACTIVASE® is for intravenous administration only. ACUTE MYOCAR-DIAL INFARCTION: Administer ACTIVASE® as soon as possible after the onset of symptoms.

The recommended dose is 100 mg administered as 60 mg (34.8 million IU) in the first hour (of which 6 to 10 mg is administered as a bolus over the first 1-2 minutes), 20 mg (11.6 million IU) over the second hour, and 20 mg (11.6 million IU) over the third hour. For smaller patients (less than 65 kg), a dose of 1.25 mg/kg administered over 3 hours, as described above, may be used.®

Although the use of anticoaquiants and antiplatelet drugs during and following administration of ACTIVASE® has not been shown to be of unequivocal benefit, heparin has been administered concomitantly for 24 hours or longer in more than 90% of patients. Aspirin and/or dipyridamole have been given either during and/or following heparin treatment.

PULMONARY EMBOLISM: The recommended dose is 100 mg administered by intravenous infusion over two hours. Heparin therapy should be instituted or reinstituted near the end of or immediately following the ACTIVASE® infusion when the partial thromboplastin time or thrombin time returns to twice normal or less.

twice normal or less

A DOSE OF 150 MG OF ACTIVASE® SHOULD NOT BE USED BECAUSE IT HAS BEEN ASSOCIATED WITH AN INCREASE IN INTRACRANIAL BLEEDING.

Reconstitution and Dilution DO NOT USE IF VACUUM IS NOT PRESENT.

ACTIVASE® should be reconstituted by aseptically adding the appropriate volume of the accompanying Sterile Water for Injection, USP to the vial. It is important that ACTIVASE® be reconstituted only with Sterile Water for Injection, USP without preservatives. Do not use Bacteriostatic Water for Injection, USP The reconstituted preparation results in a colorless to pale yellow transparent solution containing ACTIVASE® 1.0 mg/mL at approximately pH 7.3. The osmolality of this solution is approximately 215 mOSm/kg

215 mOsm/kg.

Because ACTIVASE* contains no antibacterial preservatives, it should be reconstituted immediately because ACTIVASE* contains no antibacterial preservatives, it should be reconstituted immediately because ACTIVASE* contains no antibacterial preservatives, it should be reconstituted immediately because ACTIVASE* contains no antibacterial preservatives, it should be reconstituted immediately because the contains and the should be activated and the should be visually inspected for particulate matter and discoloration prior to administration whenever solution and

visually inspected for particulate matter and discoloration prior to administration whenever solution and container permit.

ACTIVASE® may be administered as reconstituted at 1.0 mg/mL. As an alternative, the reconstituted solution may be diluted further immediately before administration in an equal volume of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to yield a concentration of 0.5 mg/mL. Either polyvinyl chloride bags or glass bottles are acceptable. ACTIVASE® is stable for up to 8 hours in these solutions at room temperature. Exposure to light has no effect on the stability of these solutions. Excessive agitation during dilution should be avoided; mixing should be accomplished with gentle swirling and/or slow inversion. Do not use other infusion solutions, e.g., Sterile Water for Injection, USP or preservative-containing solutions for further dilution.

No other medication should be added to infusion solutions containing ACTIVASE®. Any unused infusion solution should be discarded.

HOW SUPPLIED: ACTIVASE® is supplied as a sterile, lyophilized powder in 20 mg and 50 mg vials containing vacuum, each packaged with diluent for reconstitution.

Storage Store lyophilized ACTIVASE® at controlled room temperature not to exceed 30°C (86°F), or under refrigeration (2.8°E). 676-64°F). Protect the lyophilized material during extended storage from excessive exposure to light.

excessive exposure to light.

Do not use beyond the expiration date stamped on the vial REFERENCES:

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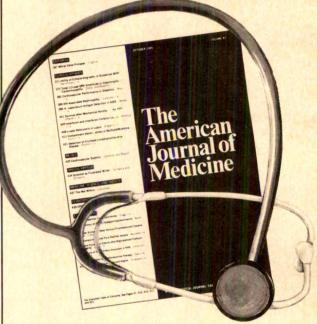
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Effects of Theophylline, Atenolol and Their Combination on Myocardial Ischemia in Stable Angina Pectoris

Filippo Crea, MD, Giuseppe Pupita, MD, Alfredo R. Galassi, MD, Hassan El-Tamimi, MD, Juan Carlos Kaski, MD, Graham J. Davies, FRCP, and Attilio Maseri, FRCP

The effects of theophylline (400 mg twice a day). atenolol (50 mg twice a day) and their combination on myocardial ischemia were studied in 9 patients with stable angina pectoris in a randomized, singleblind, triple crossover trial. Placebo was administered to the patients during the run-in and the run-off periods. A treadmill exercise test and 24hour ambulatory electrocardiographic monitoring were obtained at the end of each treatment period. Compared with placebo, theophylline significantly improved the time to onset of myocardial ischemia (1 mm of ST-segment depression) from 7.8 ± 3.7 to 9.5 \pm 3.7 minutes (p < 0.03) and the exercise duration from 9 \pm 3.4 to 10.1 \pm 3.5 minutes (p <0.04). During atenolol and during combination treatment, the time to the onset of ischemia and the exercise duration were similar (10.8 \pm 4.2 and 11.2 \pm 3.2 minutes, 11.2 \pm 3.6 and 11.5 \pm 3.2 minutes, respectively) and longer than during theophylline administration (p <0.05). Ambulatory electrocardiographic monitoring showed that, during theophylline administration, the heart rate was higher than during placebo throughout the 24 hours (p <0.05). During atenolol and during combination treatment the heart rate was similar and in both cases lower than during placebo (p <0.05). Compared with placebo, theophylline decreased the total ischemic time from 97 \pm 110 to 70 \pm 103 minutes (p <0.05). During combination treatment the total ischemic time (5.6 \pm 8.5 minutes) was not statistically different from that during atenolol administration (18 \pm 29 minutes), although it was significantly lower than that observed during theophylline administration (p <0.05). Thus, in patients with stable angina pectoris the long-term administration of theophylline improves myocardial ischemia, but to a lesser degree than atenolol. Despite the fact that atendlol abolishes the undesirable chronotropic effect of theophylline and the lat-

ter probably reduces the undesirable increase of cardiac volumes caused by atenolol, their combination does not show detectable additive effects.

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ecent studies have confirmed that acute theophylline administration results in a striking improvement in effort-induced myocardial ischemia. 1-4 We have previously demonstrated that this beneficial effect is not due to dilation of epicardial coronary arteries,^{3,4} as previously thought.⁵ We also postulated^{3,4} that the antiischemic effect of theophylline is probably mediated by redistribution of coronary blood flow from the nonischemic to the ischemic myocardium, because it is unlikely that this drug decreases myocardial oxygen consumption.^{6,7} If this hypothesis is correct, the combination of atenolol and theophylline should produce an antiischemic effect greater than each single drug because (1) their mechanisms of action appear to be complementary in so far as β -adrenergic blocking agents are thought to improve myocardial ischemia by a reduction of myocardial oxygen consumption^{8,9}; and (2) atendol might abolish the undesirable positive chronotropic action of theophylline, 6,7 whereas theophylline, by increasing venous distensibility,10 might limit the undesirable cardiac dilation caused by atenolol. 11,12 The present study is a single-blind randomized trial of the effect of theophylline, atenolol and their combination on exercise capacity and on myocardial ischemia during unrestricted daily life in 9 patients with stable angina pectoris.

METHODS

Patients: Nine men (aged 51 to 69 years, mean 60) with stable effort angina pectoris (symptom duration ranging from 5 months to 8 years, mean 2.8 years), an exercise test positive for angina and myocardial ischemia (horizontal or downsloping ST-segment depression >1 mm), and documented coronary artery disease (internal diameter reduction >70% of at least 1 major branch) participated in this trial. All patients had reproducible positive exercise test results. Coronary angiography showed 1-vessel disease in 2 patients, 2-vessel disease in 4 patients and 3-vessel disease in 3 patients. Two patients had had a myocardial infarction >3 months before the study. All patients were normotensive, in sinus rhythm and without evidence of heart failure, cardio-

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myopathy or valvular disease. No patient had evidence of left ventricular hypertrophy or conduction defects on the electrocardiogram that might have interfered with the interpretation of ST-segment changes and no patient was taking digitalis. The weight of all patients was within 2 standard deviations of the ideal weight. Four of the 9 patients who underwent the trial were ex-cigarette smokers. However, because of the history of chronic stable angina, they had been recommended to stop smoking ≥6 months before the study. All patients gave written informed consent before entry into the study, which had been approved by the Hammersmith Hospital Ethics Committee.

Study design: We compared the antiischemic effect of theophylline (400 mg twice a day), atenolol (50 mg twice a day) and their combination (at the same doses) using a randomized, single-blind, triple crossover trial of three 5-day periods. Placebo was administered to the patients during the run-in and run-off periods, each of 3-days' duration (Figure 1). Nitrates, other than sublingual nitroglycerin, and calcium blocking agents were discontinued 2 days before the run-in period, β -adrenergic blocking agents 4 days before. Objective evaluation of myocardial ischemia was obtained using exercise testing and 24-hour ambulatory electrocardiographic monitoring on day 5 of each treatment period and on day 3 of both run-in and run-off periods.

Symptom-limited, computer-assisted (CASE Marquette 12) treadmill exercise tests were performed at the same time of day, between 4 and 6 hours after last dose of treatment, using the modified Bruce protocol. A 12-lead electrocardiogram and blood pressure measurements (cuff sphygmomanometer) were obtained immediately before the test, at 1-minute intervals during the exercise, and at 5 and 10 minutes after exercise. Three electrocardiographic leads were continuously monitored before, during and after exercise.

Ambulatory electrocardiographic recordings were obtained from pre-jelled electrodes, positioned after careful skin preparation to record 2 bipolar leads (modified lead III and an anterior lead), using 2-channel am-

plitude modulated recorders (Marquette 8500). The anterior lead selected for each patient was that which had no O wave and had shown maximal ST-segment depression during exercise. All patients were instructed to continue their normal daily activity and to use nitroglycerin only for symptomatic relief.

Data analysis: For each exercise test the level of the ST segment, 60 ms after the J point, was calculated after signal averaging by a computer-assisted system in all 12 leads every minute. This provided measurements of the ST-segment level with an accuracy of 0.1 mm. The lead showing the greatest ST-segment depression was selected for analysis. The following parameters were then measured: (1) time, in minutes, to the onset of 1 mm of ST-segment depression; (2) heart rate and heart rate-blood pressure product at the onset of 1 mm ST-segment depression; and (3) total exercise time, in minutes. The exercise tests were analyzed in a blinded manner to the treatment.

The tapes obtained during ambulatory electrocardiographic monitoring were assessed using a Marquette Laser Holter System 8000. From each 24-hour period, the following data were obtained: (1) mean heart rate for each hour: (2) number of transient episodes of significant ST-segment depression (>1 mm 60 ms after the J point, lasting for at least 1 minute, with gradual onset and termination); (3) total duration of myocardial ischemia; (4) incidence of asymptomatic episodes; and (5) number of supraventricular and ventricular extrasystoles. The tapes were analyzed in a blinded fashion to the treatment. The number of anginal episodes was also obtained for each ambulatory electrocardiographic monitoring period.

The statistical analysis of the results relative to exercise tests was performed using analysis of variance; pairwise comparisons were obtained using a t test with Bonferroni correction. The results of ambulatory electrocardiographic monitoring were analyzed using the Wilcoxon rank test. The results obtained with placebo, during the run-in and the run-off periods, were averaged for comparison with the results obtained during

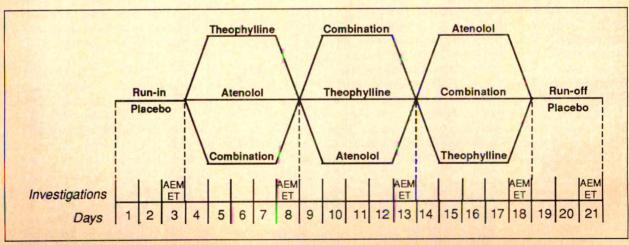


FIGURE 1. Diagrammatic representation of study design. At the end of each treatment period and of the run-in and run-off periods the exercise test (ET) and ambulatory electrocardiographic monitoring (AEM) were obtained in each patient.

the active treatment phases. A p value <0.05 was considered statistically significant. Data are presented as mean ± 1 standard deviation.

RESULTS

Adverse effects: During theophylline administration, 7 of the 9 patients had headache, particularly during the first few days of treatment; 4 reported occasional episodes of palpitation and 3 complained of heartburn. These adverse effects were less pronounced during the administration of combination treatment. In no patient was it necessary to discontinue theophylline administration because of adverse effects. No patient had obvious adverse effects during atenolol administration.

Exercise testing: During the 2 exercise tests performed with placebo, the time to 1 mm of ST-segment depression (7.7 \pm 3.6 and 7.9 \pm 3.7 minutes, difference not significant [NS]) and the exercise duration (8.8 ± 3.7 and 9.2 ± 3.1 minutes, p = NS) were similar. The heart rate (104 \pm 12 and 110 \pm 10 beats/min, p = NS) and the heart rate-blood pressure product (169 \pm 33 and 175 ± 35 beats/min/100 mm Hg, p = NS) at 1 mm of ST-segment depression were also similar.

Theophylline administration, compared with placebo, increased the time to 1 mm of ST-segment depression from 7.8 \pm 3.7 to 9.5 \pm 3.7 minutes (p < 0.03) and the exercise duration from 9 ± 3.4 to 10.1 ± 3.5 minutes (p <0.04). Both during atenolol and during combination treatment the time to 1 mm of ST-segment depression (10.8 \pm 4.2 and 11.2 \pm 3.2 minutes) and the exercise duration (11.2 \pm 3.6 and 11.5 \pm 3.2 minutes) were similar, but longer than during theophylline administration (p <0.05) (Figure 2). The latter, compared with placebo, increased heart rate at 1 mm of ST-seg-

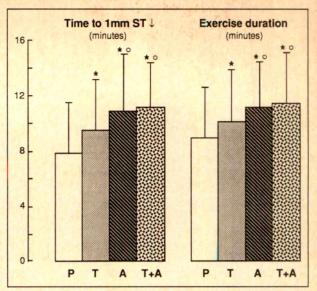
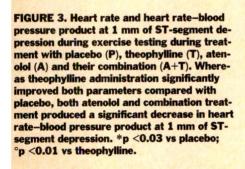
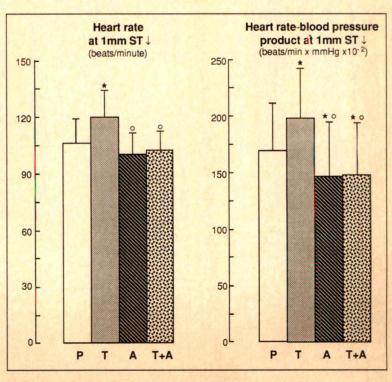


FIGURE 2. Time to 1 mm of ST-segment depression and exercise duration during treatment with placebo (P), theophylline (T), atenolol (A) and their combination (A+T). Theophylline administration, compared with placebo, significantly improved time to 1 mm of ST-segment depression and exercise duration. The beneficial effects of atenolol and of combination treatment were similar and more pronounced than those produced by theophylline. *p <0.04 vs placebo; °p <0.05 vs theophylline.

ment depression from 107 ± 10 to 120 ± 13 beats/min (p <0.005), and the heart rate-blood pressure product at 1 mm of ST-segment depression from 172 ± 34 to $193 \pm 46 \text{ beats/min} \times \text{mm Hg} \times 10^{-2} \text{ (p < 0.03)}$. During atenolol administration the heart rate-blood pressure product at 1 mm of ST-segment depression was





similar to that during combination treatment (144 \pm 38 and 147 ± 40 beats/min \times 100 mm Hg \times 10⁻²) and lower than that during placebo (p <0.03) (Figure 3). The amount of ST-segment depression at peak exercise during theophylline administration (1.4 ± 0.4 mm), during atenolol administration (1.3 \pm 0.5 mm) and during combination treatment $(1.2 \pm 0.3 \text{ mm})$ were not significantly different from those during placebo (1.5 \pm 0.4 mm).

Ambulatory electrocardiographic monitoring: The mean value of heart rate obtained for each hour of ambulatory electrocardiographic monitoring was higher during theophylline administration than during placebo, throughout the 24 hours (p <0.05). The heart rate was similar during atenolol and during combination treatment; in both cases it was lower than during placebo (p <0.05) (Figure 4).

The number of transient ischemic episodes and the total ischemic time during the run-in period were similar to those during the run-off period (2.8 \pm 2.8 and 2 \pm 1.8 episodes, 105 \pm 120 and 89 \pm 117 minutes, respectively).

During theophylline administration the number of transient ischemic episodes was similar to that during placebo (2.2 \pm 2.2 and 2.4 \pm 1.5 episodes), although the total ischemic time was significantly less (70 \pm 103 vs 97 \pm 110 minutes, p <0.05). The number and the total duration of transient ischemic episodes during atenolol administration were similar to those observed during combination treatment (1.1 \pm 1.7 and 0.5 \pm 0.7 episodes, 18 ± 29 and 5.6 ± 8.5 minutes, respectively) and lower than during placebo (p <0.05). The total ischemic time during combination treatment was significantly lower than during theophylline administration (p <0.05). The incidence of silent episodes and of supraventricular and ventricular extrasystoles was similar for the 3 different treatments (Table I). A short episode of atrial flutter was observed in 1 patient during theophylline administration.

DISCUSSION

This study shows that in patients with stable angina pectoris the long-term administration of theophylline improves myocardial ischemia during both exercise testing and ambulatory electrocardiographic monitoring. The antiischemic effect of theophylline, however, as previously reported for nifedipine and nitrates, 13-15 is less powerful than that obtained with atenolol. Surprisingly, the beneficial actions of atenolol and theophylline do not appear to be additive.

The improvement of the exercise duration and of the heart rate-blood pressure product at the onset of myocardial ischemia (1 mm of ST-segment depression) obtained in this study with long-term administration of oral theophylline administration, was less pronounced than that previously found after its intravenous administration. 1-4 This could be explained by the rather variable absorption of oral theophylline that may result in plasma drug concentrations lower than those achieved by intravenous administration. 16 In this study, plasma levels of theophylline were not measured and fixed doses of drugs were used. It is possible that a dose-escalating approach based on plasma level of theophylline might have allowed us to achieve a greater antiischemic effect. However, recent experimental evidence suggests that long-term administration of theophylline causes up-reg-

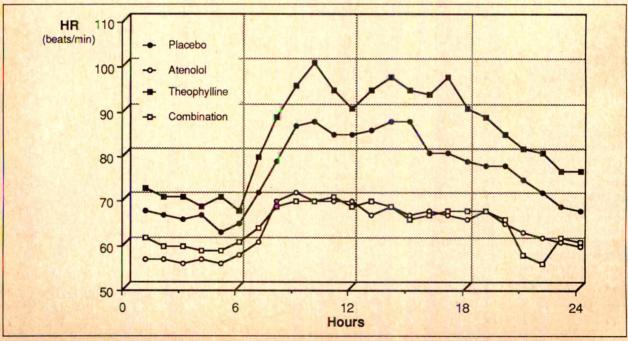


FIGURE 4. Heart rate (HR) obtained from ambulatory electrocardiographic monitoring during treatment with placebo, theophylline, atenolol and their combination. Each value represents the average heart rate relative to 1 hour. Heart rate during theophylline was higher than during placebo through the 24 hours. Heart rate during atenolol therapy was lower than during placebo therapy. During combination treatment the heart rate was similar to that during atenolol administration.

TABLE I Results of Ambulatory Electrocardiographic Monitoring

Treatment	No. of Ischemic Episodes	Silent Ischemic Episodes (%)	Total Ischemic Time (min)	No. of Ventricular Extrasystoles	No. of Supraventricular Extrasystoles
Placebo	2.4 ± 1.5	75	97 ± 110	14±17	29 ± 29
Theophylline	2.2 ± 2.2	60	70 ± 103*	129 ± 280	55 ± 99
Atenolol	1.1 ± 1.7	72	18 ± 29*	10 ± 25	33 ± 68
Combination	$0.5 \pm 0.7*$	68	5.6 ± 8.5*†	21 ± 28	22 ± 31

ulation of adenosine receptors which might progressively limit the efficacy of the drug despite optimal dosages.17

In our study, atenolol administration improved the exercise duration and decreased the total ischemic time during ambulatory electrocardiographic monitoring to a greater extent than theophylline. During atenolol treatment the heart rate-blood pressure product (an index of myocardial oxygen consumption) at the onset of exercise-induced myocardial ischemia was lower than during placebo. This index, however, does not take into account the ventricular volumes. Because it is well established that β -adrenergic blocking agents increase end-diastolic volume, which in turn increases myocardial oxygen consumption, 11,12 it is likely that the latter, during treatment with atenolol, is underestimated when considering only heart rate-blood pressure product.

The time to 1 mm of ST-segment depression and the exercise duration were slightly longer during combination treatment than during atenolol administration; however, this difference was not statistically significant. Similarly, during ambulatory electrocardiographic monitoring the total ischemic time with combination treatment was lower than with atenolol alone, but this difference, again, was not statistically significant. Such a lack of detectable additive effects appears rather difficult to explain if it is assumed that theophylline and atenolol have different mechanisms of action, particularly because each of the 2 drugs appears potentially able to counterbalance some of the undesirable adverse effects of the other. In our study, atendool abolished the positive chronotropic action of theophylline. Theophylline, on the other hand, by increasing venous distensibility, 10 may limit the increase of the cardiac volumes caused by atenolol. 11,12

The reasons for the lack of detectable additive antiischemic effects cannot be discerned from the results of our study. The fact that the beneficial effects obtained with combination treatment tend to be better than those produced by atenolol alone, suggest that a small additive effect may be present, although it does not reach statistical significance because of the small number of patients. Alternatively, one could hypothesize that theophylline and atenolol share a common mechanism of action. We have previously demonstrated that the improvement of exercise capacity obtained with theophylline is not mediated by dilation of epicardial coronary arteries and hypothesized that an important mechanism of action of theophylline could be redistribution of myocardial blood flow from the subepicardium to the subendocardium (the "Robin Hood" effect). 3,4,18 This working hypothesis is based on the experimental observation that theophylline limits the metabolic vasodilation of small coronary arteries to a greater extent in the absence than in the presence of myocardial ischemia. 19-22 Because of this differential effect, this drug could limit coronary vasodilation during exercise more in the subepicardium, which is not ischemic because of its greater coronary flow reserve, 23,24 than in the more vulnerable subendocardium. This, in turn, would increase poststenotic pressure, thus delaying the development of subendocardial ischemia.²⁵ In the present study the higher heart rate-blood pressure product at the onset of ischemia observed after theophylline appears to confirm that this drug improved myocardial perfusion during ex-

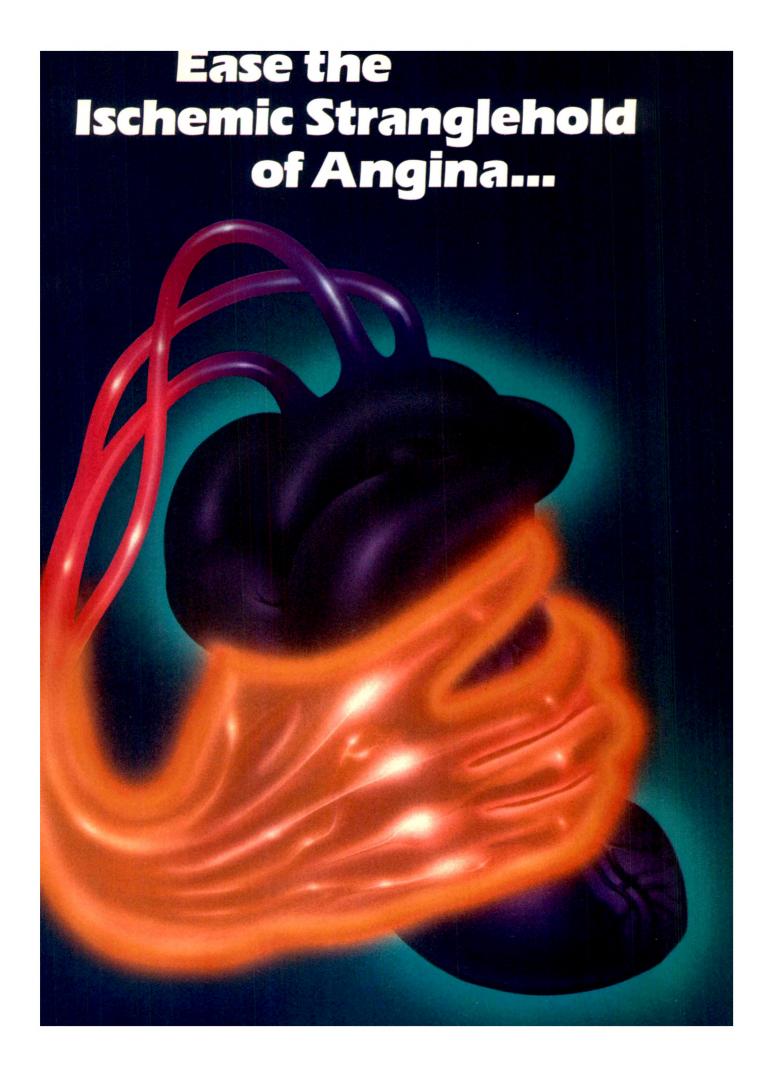
With regard to atendol, its mechanism of action is usually thought to be a reduction of myocardial oxygen consumption.9 This drug, however, may also be able to improve the transmural distribution of coronary blood flow. Gross and Winbury²⁶ observed that β -adrenergic blocking agents improve the transmural distribution of coronary blood flow at rest, as a consequence of the increased diastolic time. They also observed that this effect was absent during maximal coronary vasodilation and concluded that "the transmural redistribution is a result of the decrease in heart rate accompanied by a differential effect of β blockade on the resistance vessels of the superficial and deep regions". This conclusion is supported by the observation that β -adrenergic blocking agents can indeed cause constriction of small coronary arteries, because of the predominance of unopposed α adrenergic receptor stimulation.^{27,28} Because there is convincing experimental evidence that the stimulation of coronary α -adrenergic receptors during exercise is important in maintaining the transmural distribution of coronary blood flow, 29,30 it could well be the case, therefore, that β -adrenergic blocking agents might improve subendocardial perfusion by a selective enhancement of subepicardial coronary constriction, thus sharing with theophylline the "Robin Hood effect." The more powerful antiischemic action of atenolol could be accounted for by the fact that atenolol, but not theophylline, reduces myocardial oxygen consumption.

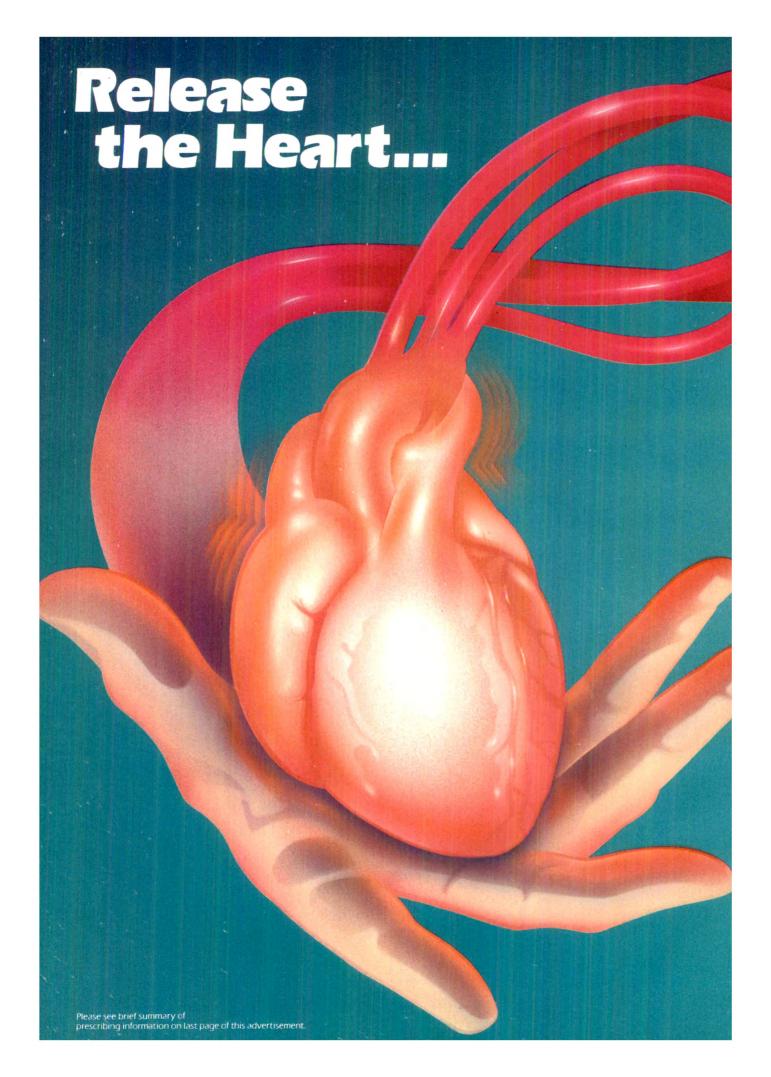
Study limitations: A limitation of this study is the use of a single-blind design. However, the selection of objective end points (as time to and heart rate-pressure product at 1 mm of ST-segment depression during exercise testing, and number and duration of ischemic episodes during ambulatory electrocardiographic monitoring), the computerized assessment of the electrocardiograms and the analysis of results blind to the treatment should substantially overcome the drawbacks of the single-blind design. Another possible criticism to our study is that the exercise tests performed with placebo were not randomized. However, because they were performed during both the run-in and run-off periods and produced similar results, it is very unlikely that the training effect³¹ could have influenced the results of the exercise tests performed during the nonrandomized part of our study.

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Brief Summary



Capsules

For oral use

MECHANISM OF ACTION: CARDENE is a calcium entry blocker which inhibits the transmembrane influx of calcium ions into cardiac muscle and smooth muscle without changing serum calcium concentrations. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. The effects of CARDENE are more selective to vascular smooth muscle than cardiac muscle. In animal models, CARDENE produces relaxation of coronary vascular smooth muscle at drug levels which cause little or no negative inotropic effect.

CONTRAINDICATIONS: Patients with hypersensitivity to the drug. Because part of the effect of CARDENE is secondary to reduced afterload, the drug is also contraindi-cated in patients with advanced aortic stenosis.

WARNINGS: Increased Angina: About 7% of patients in short termplacebo-controlled angina; About 7% of patients in short termplacebo-controlled angina trials have developed increased frequency, duration or severity of angina on starting CAPDENE or at the time of dosage increases, compared with 4% of patients on placebo. Comparisons with beta-blockers also show a greater frequency of increased angina, 4% vs 1%. The mechanism of this effect has not been established. [See ADVERSE REACTIONS.]

Use in Patients with Congestive Heart Failure: Although preliminary hemodynamic studies in patients with congestive heart failure have shown that CARDENE reduced afterload without impairing myocardial contractility, it has a negative inotropic effect in vitro and in some patients. Caution should be exercised when using the drug in congestive heart failure patients, particularly in combination with a beta-blocke

Beta-Blocker Withdrawal: CARDENE is not a beta-blocker and gives no protection against the dangers of abrupt beta-blocker withdrawal, any such withdrawal should be by gradual reduction of the dose of beta-blocker, prefera-

PRECAUTIONS: General: Blood Pressure: Careful monitoring of blood pressure during the initial administration and titration of CARDENE is suggested. CARDENE may occasionally produce symptomatic hypotension Caution is advised to avoid systemic hypotension when administering the drug to patients who have sustained an acute cerebral infarction or hemorrhage. Because of prominent effects at the time of peak blood levels, initial titration should be performed with measurements of blood develve at trouble first before with measurements of blood pressure at trough (just before the next dose) and at peak effect (1–2 hours after dosing).

Use in patients with impaired hepatic function: The drug should be used with caution in patients having impaired liver function or reduced hepatic blood flow. Patients with severe liver disease developed elevated blood levels (4-fold

increase in AUC) and prolonged half-life (19 hours) of CARDENE.

Use in patients with impaired renal function: Mean plasma-concentrations, AUC. and Cmax were approximately 2-fold higher in hypertensive mildly renally impaired patients treated with CARDENE than in healthy controls. Doses in these patients must be adjusted.

Drug Interactions: Cimetidine: Cimetidine increases CARDENE plasma levels. Patients receiving the two drugs concomitantly should be carefully monitored.

Digoxin: Some calcium blockers may increase the concentra-tion of digitalis preparations in the blood. CARDENE usually does not alter the plasma levels of digoxin, however, serum digoxin levels should be evaluated after concomitant therapy with CARDENE is initiated

Maalox: Co-administration of Maalox TC had no effect on CARDENE absorption

Fentanyl Anesthesia: Severe hypotension has been reported during fentanyl anesthesia with concomitant use of a beta-blocker and a calcium channel blocker. Even though such interactions were not seen during clinical studies with CARDENE, an increased volume of circulating fluids might be required if such an interaction were to occur.

Cyclosporine: Concomitant administration of CARDENE and cyclosporine results in elevated plasma cyclosporine levels. Plasma concentrations of cyclosporine should therefore be closely monitored, and its dosage reduced accordingly, in patients treated with CARDENE.

When therapeutic concentrations of furosemide, propranolol, dipyridamole, warfarin, quimidine, or naproxen were added to human plasma (in vitro), the plasma protein binding of CARDENE was not altered

Carcinogenesis, Mutagenesis, Impairment of Fertility: Rats treated for 2 years had a dose-dependent increase in thyroid hyperplasia and neoplasia. Mice treated for 18 months had no neoplasia or thyroid changes and dogs treated for 1 year had no thyroid pathology. There is no evidence of effects on thyroid function (plasma T4, TSW) in man. There was no evidence of mutagenic potential in a battery of tests, and no impairment of fertility in male or female rats.

Pregnancy: Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. CARDENE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is recommended that women who wish to breast-feed should not take this drug

Pediatric Use: Safety and efficacy in patients under the age of 18 have not been established.

Use in the Elderly: Pharmacokinetic parameters did not differ between elderly hypertensive patients (≥65 years) and healthy controls after one week of CARDENE 20 mg TID. Plasma CARDENE concentrations in elderly hypertensive patients were similar to plasma concentrations in healthy young adult subjects when CARDENE was administered at doses of 10, 20 and 30 mg TID, suggesting that the pharmacokinetics of CARDENE are similar in young and elderly hypertensive patients. No significant differences in responses to CARDENE have been observed in elderly patients and the

general adult population of patients who participated in clinical studie

ADVERSE REACTIONS: In short-term (up to three ADVERSE REACTIONS: In short-term (up to three months) studies 1,910 patients received CARDENE alone or in combination with other drugs. In these studies, adverse events were generally not serious but occasionally required dosage adjustment. Feak responses were not observed to be associated with adverse effects during clinical trials, but physicians should be aware that adverse effects associated with decreases in blood pressure (tachycardia, hypotension, etc.) could occur around the time of the next effect. etc.) could occur around the time of the peak effect.

Angina: The most common adverse events include pedal Angina: The most common adverse events include pedal edema and dizziness in about 7% of patients; headache, asthenia, flushing and increased angina in about 6%; palpitations in about 3%, and nausea and dyspepsia in about 2%. Adverse events occurring in about 1% of patients include dry mouth, somnolence, rash, tachycardia, myalgia, other edema and paresthesia. Sustained tachycardia, syncope, constipation, dyspnea, abnormal ECG, malaise, nervousness and tremor occurred in less than 1% of patients.

In addition, adverse events were observed which are not In addition, adverse events were observed which are not readily distinguishable from the natural history of the atherosclerotic vascular disease in these patients. Adverse events in this category each occurred in <0.4% of patients receiving CARDENE and included myocardial infarction, atrial fibrillation, exertional hypotension, pericarditis, heart block, cerebral ischemia and ventricular tachycardia. It is possible that some of these events were drug-related.

Hypertension: The most common adverse events include flushing in about 10% of patients, headache and pedal edema in about 8%; asthema, palpitations and dizziness in about 4%; tachycardia in about 3%; nausea in about 2%; and somno-lence in 1%. Dyspepsia, insomnia, malaise, other edema, abnormal dreams, dry mouth, nocturia, rash and vomiting occurred in less than 1% of patients.

Additionally, the following rare events have been reported: infection, allergic reaction, hypotension, postural hypotension, atypical chest pain, peripheral vascular disorder, ventricular extrasystoles, ventricular tachycardia, sore throat, abnormal liver chemistries, arthralgia, hot flashes, vertigo, hyperkinesia, impotence, depression, confusion, anxiety, thinitis, sinusitis, timnitus, abnormal vision, blurred vision, increased urgary frequency. increased urinary frequency.

More detailed professional information available on request. U.S. Patent No. 3,985,758

References: 1. Pepine C. Nicardipine, A new calcium channel blocker: Role for vascular selectivity. Clin. Cardiol. 1989;240-246. 2. Whiting RL. Animal pharmacology of nicardipine and its dinicial relevance. Am J Cardiol. 1987;59:33-8J. 3. Eurlew BS, Gheorghiade M, Jafri SM, et al. Acute and chronic hemodynamic effects of nicardipine hydrochloride in patients with heart failure. Am Heart J. 1987;114:793-804. 4. Slike B. Verma SP, Frais MA, et al. Haemodynamic analysis of the effects of nicardipine and Haemodynamic analysis of the effects of nicardipine and metoprolol alone and in combination in coronary artery disease. Eur Heart J. 1985;6:930-938. 5. Douard H, Mora B, Broustet J-P. Comparison of the anti-anginal efficacy of nicardipine and nifedipine in patients receiving atenolol: a randomized, double-blind, crossover study. Int. J. Cardiol. 1989;22:357-363.



Transient Left Ventricular Cavitary Dilation During Dipyridamole-Thallium Imaging as an Indicator of Severe Coronary Artery Disease

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Transient left ventricular (LV) cavitary dilation during dipyridamole-thallium imaging was reported in 45 of 510 (9%) consecutive patients referred for dipyridamole-thallium imaging, Clinical and hemodynamic effects observed during dipyridamole infusion were not predictive of transient cavitary dilation on the thallium images. Coronary angiography was performed in 32 of the 45 patients: 75% had either left main, 3-vessel or "high-risk" 2-vessel coronary artery disease. Although 25 of 45 patients (56%) with transient cavitary dilation were either asymptomatic or had only grade 1/4 effort angina, 16 of 25 patients (64%) not referred for coronary revascularization sustained a cardiac event during a mean follow-up of 12 months. Most events were cardiac deaths (75%) and 87% of events occurred within 4 months of the test. Noncardiac surgery was performed in 187 of the 510 patients. The postoperative cardiac event rate was 2% in the 101 patients with normal scans or fixed defects, 19% in 75 patients with reversible perfusion defects and 58% in 12 patients with reversible cavitary dilation (p <0.0001). Thus, transient LV dilation during dipyridamole-thallium imaging is a marker of severe underlying coronary artery disease, denotes a poor prognosis and predicts a high risk of postoperative cardiac complications in patients who undergo noncardiac surgery.

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yocardial perfusion imaging after pharmacologic coronary vasodilation with intravenous dipyridamole is a reliable alternative to the standard treadmill test in patients unable to exercise to an adequate heart rate. Dipyridamole-thallium imaging is routinely used in suspected and known patients with coronary artery disease to detect underlying stenoses,2 for cardiac risk assessment before noncardiac surgery, and for risk stratification after myocardial infarction.4 In a series of 510 consecutive patients who underwent dipyridamole-thallium imaging, 45 developed dipyridamole-induced transient left ventricular (LV) dilation. This study defines the clinical and angiographic correlates of this phenomenon, the hemodynamic response to dipyridamole infusion in these patients, and their cardiac event rate during follow-up.

METHODS

Study population: The initial study group consisted of 510 consecutive patients referred for dipyridamole-thallium imaging. Their average age (mean \pm standard deviation) was 61 \pm 10 years (range 30 to 85); 281 were men and 229 women. Transient LV cavitary dilation was reported in 45 patients, but the decision to investigate the patient further was left to the referring physician.

Dipyridamole infusion protocol: The dipyridamole infusion protocol was described in detail in a previous report.³ Dipyridamole was infused at a rate of 0.14 mg/kg/min over 4 minutes up to a maximal dose of 50 mg. After the infusion, the patient stood and walked in place for 2 minutes. There were no major irreversible side effects from dipyridamole in the 510 patients.

Thallium-201 myocardial imaging: The first image was acquired in the best septal view, followed by the left anterior oblique 70° view, and the anterior view. Delayed images were obtained 4 hours after thallium injection. Preset time 8-minute images were acquired in each of the 3 views. For each scintigraphic study, the following images were displayed: analog images, interpolative background subtracted images, circumferential profiles and washout rate analysis. All myocardial scintigraphic images were interpreted by 2 experienced observers without prior knowledge of patient history or coronary anatomy. Infrequent disagreements in interpretation were resolved by consensus.

A fixed defect was defined as an initial perfusion defect with no redistribution on delayed images, plus

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electrocardiographic evidence of a necrosis in the corresponding segment or with a clinical history of myocardial infarction and documented elevation of cardiac enzymes (when available) proportional to the size of the observed perfusion defect. Otherwise, we usually administered 1 mCi of thallium-201 at rest before redistribution images, or acquired 24-hour delayed thallium images, or performed a radionuclide gated equilibrium ventriculogram (MUGA scan), preferably during continuous intravenous nitroglycerin infusion to confirm the presence of scar tissue.

Scans were divided into 3 segments for each view. For semiquantification, the myocardium was divided into 6 regions taking into account anatomic overlap of the segments (Figure 1). All regional perfusion defects were graded according to a 3-point scale (reversibility index): grade 0/3 being normal and grade 3/3 the most severe. Visualization of interpolated background-subtracted images minimized interobserver variation in the grading system. The indexes used to semiquantify the extent and severity of reversible defects are described in Appendix 1. This is an adaptation of the scintigraphic technique used by Ladenheim et al⁵ to assess the extent and severity of exercise-induced myocardial ischemia.

Left ventricular cavitary dilation: The LV cavity was measured in the best septal view on the immediate postdipyridamole and redistribution analog images. A patient was considered to show transient cavitary dilation when the largest short-axis LV diameter in the best septal view on the early images was >15% larger than on the delayed images. The number of views showing cavitary dilation, and the presence of transient dilation of the LV outer borders (external LV dilation) were also noted.

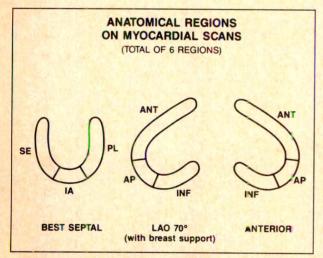


FIGURE 1. The left ventricle was divided into 3 segments in each view, for a total of 9 segments. However, the final compilation of scintigraphic indexes was based on only 6 regions, taking into account geometric overlap of the segments. When scintigraphic indexes for overlapping segments differed in magnitude, the segment with the most severe and reversible perfusion defect was considered as representative of the region. ANT = anterior; AP = apical; IA = inferoapical; INF = inferior; LAO = left anterior oblique; PL = posterolateral; SE = septal.

Coronary angiography: Selective coronary angiography was interpreted by 2 independent observers (a cardiologist and a radiologist). Significant coronary stenoses were those ≥50% luminal diameter narrowing in a major vessel or a primary branch.

Outcome after noncardiac surgery: Of the 510 patients, 187 underwent noncardiac surgery, with antianginal medication when there was thallium redistribution. All patients who underwent noncardiac surgery were followed postoperatively for evidence of a cardiac event up to discharge from hospital. Only cardiac death (sudden, or due to an acute infarction) and acute myocardial infarction before discharge from the hospital were accepted as end points. Acute myocardial infarction was diagnosed when ≥2 of the following 3 criteria were met: (1) recent episode of characteristic chest pain that lasted >30 minutes; (2) transient increase above the upper limit of normal of total serum creatine kinase and its myocardial isoenzyme subfraction (MB-CK), related temporally to the episode of chest pain; and (3) Minnesota code criteria^{6,7} for definite or probable myocardial infarction accompanied by evolving ST- and Twave changes.

Patient prognosis: All patients were contacted by phone by a physician, unless it was clearly recorded in the hospital chart that the patient had been referred for coronary revascularization or had sustained a cardiac event.

Statistical analysis: Correlation between clinical parameters, dipyridamole-induced chest pain, minor side effects, and variations in heart rate and blood pressure were done using chi-square and analysis of variance, as were correlations between clinical parameters, the Dripps-American Surgical Association score, the Goldman Cardiac Risk Index score, scintigraphic indexes and postoperative cardiac events. All values are mean ± standard deviation.

RESULTS

Patient population: The clinical features of patients with transient cavitary dilation are summarized in Table I. No patient had grade 3 or 4 angina pectoris.

Clinical and hemodynamic effects of dipyridamole infusion: The clinical and hemodynamic effects of dipyridamole infusion in the group of 510 patients separated in subgroups with normal scans or fixed defects (n = 223), reversible perfusion defects excluding patients with transient LV cavitary dilation (n = 242), and patients with transient cavitary dilation (n = 45) are summarized in Table II. The appearance of typical chest pain correlated with the presence of both reversible perfusion defects and transient LV dilation. There was no statistical correlation between the appearance of atypical chest pain, dyspnea, ST-segment depression in lead II, variation in heart rate or systolic blood pressure or minor adverse effects, and the presence of either reversible defects or transient LV cavitary dilation.

Myocardial perfusion images: Scintigraphic data, including the location and severity of reversible defects, semiquantitative indexes of severity and extent, and coronary pattern, are detailed in Table III and Figure 2.

TABLE I Clinical Features of 45 Patients with Transient Left Ventricular Cavitary Dilation

Clinical Parameter	No. (%)
Number of men	31 (69)
Age (mean ± SD)	62.9 ± 13.3
History of coronary artery disease	37 (82)
Average number of risk factors	1.93
Smoking	33 (73)
Hypertension	20 (44)
Hypercholesterolemia	9 (20)
Diabetes	15 (33)
Family history	9 (20)
Chest pain syndrome	
Asymptomatic	22 (49)
Angina grade 1/4	3(7)
Angina grade 2/4	18 (40)
Atypical chest pain	2(4)
Previous myocardial infarction	23 (51)
Clinical signs of heart failure	3(7)
Previous episodes of pulmonary edema	9 (20)
Electrocardiography	
Q waves	9 (20)
Left ventricular hypertrophy	12 (27)
ST-T abnormalities	28 (62)
Left bundle branch block	3(7)
Radionuclide ventriculography (in 36 patients)	
First-pass gated RVEF: 36/36 (100%) normal	
Equilibrium gated LVEF:	
Normal	18 (50)
40–50%	10 (28)
30–40%	6(17)
<30%	2(6)

Transient LV dilation was misdiagnosed on 1 scan owing to a technical artifact (uniformity correction artifact due to a faulty scintillation camera): a repeat dipyridamole-thallium test, the coronary angiogram, the contrast ventriculogram and the 1-year follow-up were all normal, and this patient was excluded from the quantitative scintigraphic and prognostic studies. The cavitary dilation was observed only in the best septal view in 18% of patients, in the first 2 views in 2%, and in all 3 views in 80%. In addition, transient external dilation of the left ventricle was observed in 24 (56%) of the patients with transient cavitary dilation. Transient cavitary dilation was visible in all 3 views in 95% of patients with concomitant external dilation, and in 67% of patients without external cavitary dilation.

Coronary angiography: Thirty-two patients with transient cavitary dilation underwent coronary angiography. One had a normal study (the patient with the technical artifact), one had an idiopathic dilated cardiomyopathy (normal coronary arteries with global LV dysfunction and an ejection fraction of 35%, down to 24% 1 month later), 9 had left main coronary artery disease, 8 had 3-, 9 had 2- and 4 had 1-vessel disease (left anterior descending coronary artery in 2, right coronary artery in 1, circumflex coronary artery in 1). Of the 9 patients with 2-vessel disease, 7 had ≥70% stenosis of the left anterior descending coronary artery. Twenty-eight patients underwent LV pressure recordings and 22 had contrast ventriculography. The average

TABLE II Clinical and Hemodynamic Effects of Dipyridamole Infusion in 510 Patients

	Normal Scan or Fixed Defect (n = 223)	Reversible Defect(s)* (n = 242)	Transient LV Dilation (n = 45)
Typical CP	10 (4.5)	40 (17)	10 (22)
Atypical CP	25 (11)	22 (9)	3(7)
Dyspnea	6(3)	20(8)	4(9)
ST depression	7 (3)	17 (7)	5(11)
AVE SYS BP DECR	13±12	13±16	14±17
AVE DIPY DOSE	37.5	39.7	39.6
Minor symptoms	40 (18)	56 (23)	5(11)

* Includes all patients with reversible perfusion defect(s) except for those with transient dipyridamole-induced cavitary left ventricular dilation.

AVE DIPY DOSE = average dipyridamole dose (mg) based on the administration of 0.5 mg/kg dipyridamole over 4 minutes up to a maximum of 50 mg; minor symptoms include headache, dizziness, flushing, nausea and vomiting; AVE SYS BP DECR = average dipyridamole-induced decrease in systolic blood pressure (mm Hg); CP = chest pain; LV = left ventricular; ST depression = dipyridamole-induced ST-segment depression in lead II.

TABLE III Scintigraphic Data in 45 Patients with Transient

	No. of Pts.	Reversibility	
Segment	(n = 45 [%])	Index	
Location	and Severity of Rev	ersible Defects	
Anterior	31 (69)	1.4 ± 1.1	
Apical	32 (71)	1.6 ± 1.2	
Septal	32 (71)	1.5 ± 1.1	
nferior	26 (58)	1.2 ± 1.2	
nferoapical	23 (51)	0.8 ± 1.2	
Posterolateral	17 (38)	1.2 ± 1.2	
		Range	
ndex	±SD	Min Max	
Semiquantit	ative Indexes of Sev	erity and Extent*	
Reversible extent	3.6 ± 1.5	0 6	
Significant reversible	3.4 ± 1.5	0 6	

 $^{7.7 \}pm 3.8$ * See Appendix for description of indexes. All values are mean ± standard devi-

 2.3 ± 0.8

0

0

3

16

Maximal reversibility

Summed reversibility

LV end-diastolic pressure at rest was 23 \pm 9 mm Hg, with an average increase of 4 mm Hg after contrast ventriculography. Angiographic data are summarized in Figure 3.

Outcome: One patient died of carcinomatosis 3 months after the test and was excluded from further prognostic analysis. Nine patients with an average follow-up of 12 months were stable and event free. There were 16 cardiac events (11 cardiac deaths and 5 nonfatal myocardial infarctions). One patient was lost to follow-up. Seventeen patients were referred for coronary revascularization (3 for coronary angioplasty and 14 for coronary artery bypass grafting). Twelve of the 16 patients who sustained cardiac events also underwent equilibrium radionuclide ventriculography at the time of dipyridamole imaging. The global LV ejection fraction was normal in 4, decreased to 40 to 50% in 3, 30 to 40% in 3 and below 30% in 1 patient. The outcome of all 45 patients is illustrated in Figure 4.

Outcome after noncardiac surgery: One hundred eighty-seven of the entire series of 510 patients underwent noncardiac surgery (vascular surgery in 125 and general surgery in 62). There were 22 postoperative cardiac events. Because most patients with transient LV cavitary dilation also had reversible perfusion defects, frequently involving the anterior segment (71%) (Table III and Figure 2), the incidence of postoperative events was compiled in 4 scintigraphic subgroups: normal scan or fixed defect(s) (n = 101), reversible perfusion defect(s) but no transient LV dilation (n = 75), a revers ible defect of the anterior segment (with or without oth er reversible defects, but without transient LV cavitary dilation) (n = 19), and transient LV cavitary dilation (1 = 12). The latter 3 scintigraphic signs were all inde pendent predictors of postoperative cardiac events (1 <0.0001). None of the clinical parameters of the 18 patients, including age, gender, history of coronary dis ease, presence and number of risk factors (hypertension smoking, hypercholesterolemia, family history or diabe

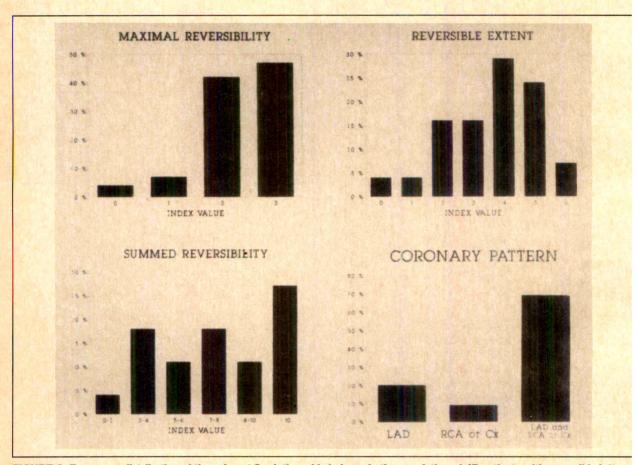


FIGURE 2. Frequency distribution of the value of 3 scintigraphic indexes in the population of 45 patients with reversible left ventricular cavitary dilation. The scintigraphic coronary pattern is depicted on the bottom right graph. Cx = circumflex coronary artery; LAD = left anterior descending artery; RCA = right coronary artery.

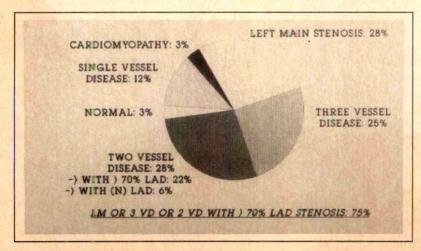


FIGURE 3. Sumary of the coronary anatomy of 32 patients with transient left ventricular cavitary dilation who underwent coronary angiography. LAD = left anterior descending artery.

tes), history of a previous myocardial infarction, resting electrocardiographic abnormalities, type of surgery, intra- versus extraabdominal surgery, the Dripps-American Surgical Association class,8 the Goldman multifactorial risk index score9 or the Detsky multifactorial risk index score¹⁰ correlated with postoperative outcome. Results of postoperative outcome in different scintigraphic subgroups are summarized in Figure 5.

Natural history of patients with transient left ventricular cavitary dilation: Excluding 7 patients with postoperative cardiac events and 17 patients referred for coronary revascularization, the natural history of patients with transient LV cavitary dilation was studied in 18 patients (Figure 6). Nine patients were event free an average of 12.2 months after dipyridamole-thallium testing. All 9 cardiac events were deaths (6 fatal myo-

FIGURE 4. Outcome of 45 patients with transient left ventricular cavitary dilation. MI = myocardial infarction.

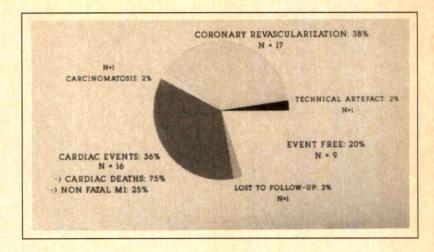


FIGURE 5. Postoperative cardiac event rate in 187 patients who underwent noncardiac surgery. The patients were separated into 4 scintigraphic subgroups. Note that patients with transient left ventricular (LV) cavitary dilation were excluded from the groups with reversible defects and anterior wall defects and classified separately. Patients with anterior wall defects could also have reversible defects in other segments. The subgroup with reversible defects also includes patients with anterior wall defects; thus, the total number of patients in all subgroups is higher than 187.

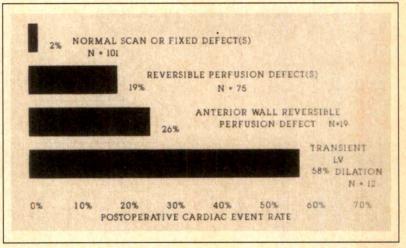
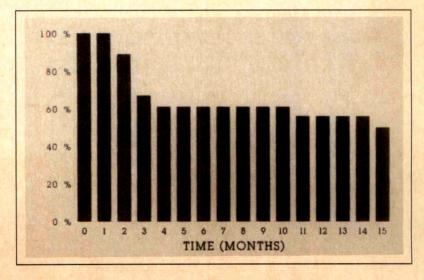


FIGURE 6. Natural history of 18 patients with transient left ventricular cavitary dilation who were not referred for coronary revascularization and did not sustain a postoperative cardiac event. Percent patient survival is depicted on the Y axis.



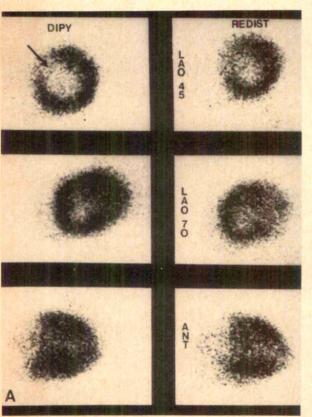
cardial infarctions and 3 sudden deaths) and occurred an average of 4.4 months after the test, with 87% of deaths occurring within the first 4 months.

Scintigraphic pattern: There was no correlation between the scintigraphic pattern (number of views that showed cavitary dilation, presence of concomitant external LV dilation) and either the coronary anatomy, postoperative outcome or natural history.

DISCUSSION

Dipyridamole-induced coronary vasodilation has been shown to be as reliable as exercise testing for the detection of coronary stenoses.1 However, there is an ongoing search for new clinical and scintigraphic criteria of diagnostic or prognostic value to refine the interpretation of the test beyond the 3 categories of normal scan, fixed defect(s) and reversible defect(s).

Clinical signs: In contrast to exercise testing, where exertional hypotension is a useful sign, variations in heart rate and blood pressure during dipyridamole-thallium imaging are of little diagnostic use and did not correlate with the presence of reversible defects in the group of 510 patients. In a previous study, we did not find any correlation between the appearance of chest pain after dipyridamole infusion and the presence of coronary artery disease.2 When 12-lead tracings are obtained, transient ST-segment depression is seen in 15 to 25% of patients, 11 but is of little prognostic value. 12 Auscultation should be routinely performed during the test, searching for evidence of ischemic pulmonary con-



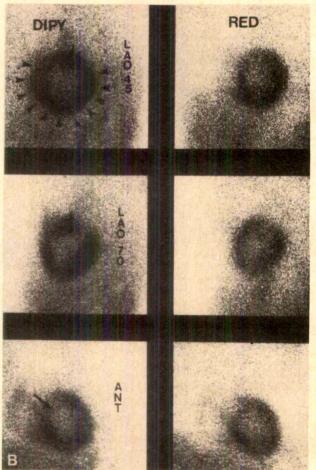


FIGURE 7. Scintigraphic pattern of left ventricular (LV) cavitary dilation on the immediate postdipyridamole (DIPY) (left) and redistribution (REDIST) (right) images in the best septal left anterior oblique (LAO) 40 to 45°, LAO 70° and anterior (ANT) views. A, a 60-year-old man who underwent dipyridamole-thallium imaging for cardiac risk assessment before elective resection of an aneurysm of the abdominal aorta had grade 2/4 effort angina and no previous history of myocardial infarction. There is reversible dilation of the LV cavity seen in the best septal view (arrow), but no reversible segmental defects and no external LV dilation. Note that the whole left ventricle appears globular in shape on the immediate postdipyridamole best septal image, and more ballistic in shape on the redistribution image. The coronary angiogram showed a 70% stenosis of the left main coronary artery, a 95% stenosis of the right coronary artery, an 80% stenosis of the left anterior descending coronary artery and a 60% stenosis of the circumflex coronary artery. LV end-diastolic pressure was increased to 35 mm Hg and the contrast ventriculogram was normal. The patient underwent triple coronary artery bypass grafting followed by uneventful resection of the abdominal aortic aneurysm 2 months later. B, a 55-year-old woman with a history of claudication was admitted for elective aortic replacement. She denied having any angina or previous myocardial infarction. The thallium images show both cavitary (arrow) and external (arrowheads) LV dilation visible in all 3 views and reversible perfusion defects of the anterior, apical and septal segments. Note the globular shape of the left ventricle on the immediate postdipyridamole best septal image and the ballistic shape on the redistribution image. The coronary angiogram showed a 60% stenosis of the right coronary artery, a 100% obstruction of the left anterior descending coronary artery, and a 75% stenosis of the circumflex coronary artery, with an end-diastolic pressure increased to 35 mm Hg. The contrast ventriculogram was not recorded, but an equilibrium radionuclide ventriculogram was normal with LV ejection fraction of 56%. The patient was referred for coronary artery bypass grafting.

gestion¹³ or reversible mitral regurgitation due to ischemic papillary muscle dysfunction.¹⁴

Mycardial perfusion images: The value of tomography, ¹⁵ and of quantification of segmental myocardial ¹⁶ and pulmonary ¹⁷ thallium uptake and washout is still controversial. We have previously shown that semi-quantitative evaluation of the severity and extent of reversible perfusion defects correlates well with the occurrence of postoperative cardiac complications after non-cardiac surgery.³

Transient left ventricular cavitary dilation: Transient LV cavitary dilation is easily recognized with the naked eye on the analog thallium images in the best septal view, and cavitary measurements are only used to confirm the visual impression. This finding was observed in 9% of 510 consecutive patients referred for dipyridamole-thallium images in this study. None of the clinical or hemodynamic changes observed during the dipyridamole infusion were predictive of transient cavitary dilation on thallium images. The reversible cavitary dilation was usually, but not always, accompanied by multiple reversible perfusion defects.

Most patients had severe coronary artery disease: 75% had either left main or 3-vessel or "high-risk" 2-vessel coronary artery disease (including ≥70% luminal narrowing of the left anterior descending coronary artery) and the average LV end-diastolic pressure was increased to 23 mm Hg.

Prognostic implications: Patients with dipyridamole-induced transient LV cavitary dilation had a grim prognosis; 64% sustained a cardiac event (75% cardiac deaths and 25% nonfatal myocardial infarctions) and 87% of these events occurred within 4 months of the test. But prognostic indicators are only useful if the poor prognosis was not already obvious clinically; i.e., it is important to establish that patients with reversible LV dilation were not the "sickest of the sick" clinically. This is demonstrated by the fact that most of the 45 patients were either asymptomatic (49%) or had only mild effort angina clinically, 50% of patients had a normal ejection fraction, 78% of patients had an ejection fraction >40%, and only 7% had clinical signs of heart failure.

The postoperative cardiac event rate was a prohibitive 58% for patients in the group who underwent non-cardiac surgery. These high-risk patients could not have been identified clinically: There was no statistical correlation between individual clinical parameters, the Dripps-American Surgical Association class, the Goldman score, the Detsky score, and postoperative outcome. This underscores the difficulty in clinically evaluating patients who spontaneously restrict their activity in response to peripheral vascular or other limitating diseases and are referred for dipyridamole-thallium imaging instead of exercise testing.^{3,18}

Mechanism: The mechanism of transient LV cavitary dilation is unknown and more experimental data are necessary to determine its nature. Transient LV cavitary dilation has also been described during exercise testing and shown to correlate with multivessel disease, but the mechanism has never been satisfactorily ex-

plained.¹⁹ The observation that the postoperative cardiac event rate was 3 times higher in patients with transient cavitary dilation than in patients with reversible defects, and more than twice as high as in those with anterior reversible defects, suggests that transient LV cavitary dilation is not simply an illusion that results from viewing a reversible segmental perfusion defect head-on. Additional evidence against this possibility is the fact that transient LV cavitary dilation was observed in all 3 views in 80% of patients.

The most likely explanation for the transient cavitary dilation is either diffuse subendocardial relative hypoperfusion or ischemia, or transient ischemic LV dysfunction. Examples that may represent these 2 patterns are illustrated in Figure 7, A and B. However, neither explanation is completely satisfactory and >1 mechanism may be involved. Dipyridamole-induced ischemic LV dysfunction has previously been demonstrated by radionuclide ventriculography, 13,20 and is the most plausible explanation when concomitant external and cavitary LV dilation are observed. A globular-shaped left ventricle on the immediate postdipyridamole best septal view, with a ballistic shape on the redistribution image, may also signify transient LV dysfunction. In 24 of the 25 patients with dilation of the external border, the LV cavitary dilation was visible in all 3 views. Because the 3 views are acquired sequentially and 8 minutes are required for each view, LV dysfunction must persist for ≥25 minutes.

In patients with reversible cavitary dilation during dipyridamole-thallium testing, repeat testing with technetium-99m - methoxy - isobutyl - isonitrile (99m - Tc-MIBI), a new myocardial perfusion agent which can also be used for first-pass ventriculography,²¹ will probably clarify the mechanism. The first-pass ventriculogram obtained immediately after dipyridamole infusion would demonstrate dipyridamole-induced LV dysfunction. Because 99m-Tc-MIBI is injected right after the infusion, whereas images are acquired 2 hours later, any cavitary dilation present on 99m-Tc-MIBI images would likely represent diffuse subendocardial relative hypoperfusion or ischemia.

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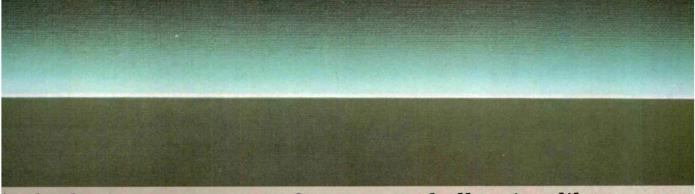
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APPENDIX

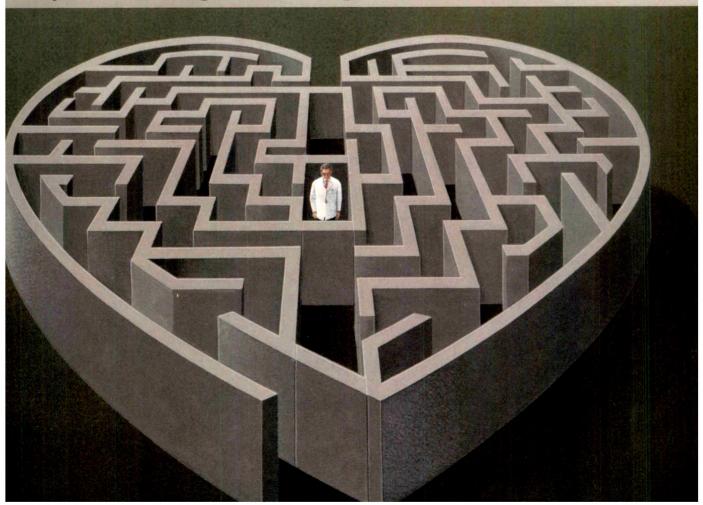
Definition of indexes for severity and extent: EXTENT: The myocardium is divided into 6 anatomic regions. The extent refers to the number of regions displaying a given characteristic (range from 1 to 6); (1) reversible extent: the number of anatomic regions that display thallium redistribution (range 0 to 6); (2) significant reversible extent index: the number of anatomic regions that display thallium redistribution (range 0 to 6), ignoring mild grade 1/3 reversible defects in infarcted regions with a grade 2/3 residual defect on delayed views.

REVERSIBILITY: the difference in severity scores in a given anatomic region between the immediate postdipyridamole and the delayed images (range 0 to 3; measured for each of the 6 regions); (1) summed reversibility index: the sum of the reversibility scores measured for each of the 6 regions (range 0 to 18); (2) maximal reversibility index: the highest reversibility score among the 6 regions (range 0 to 3).

CORONARY PATTERN: coronary pattern as estimated from the scintigrams. 1 = left anterior descending coronary artery pattern; 2 = right coronary artery or circumflex coronary artery pattern: 3 = 1 and 2.



Arrhythmia management often poses a challenging dilemma





Opens the wa

Class I, membrane-stabilizing agent for life-threatening ventricular arrhythmias— "best fits class IA of the Vaughan Williams classification..."

Ventricular arrhythmia suppression comparable to quinidine²

Low incidence of proarrhythmia^{3,4}

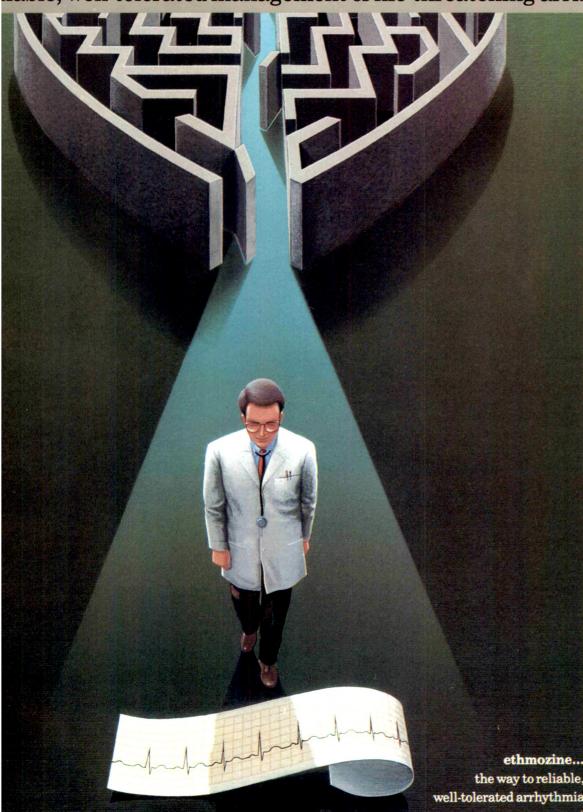
Proven record in patients with left ventricular (LV) dysfunction⁵

Well tolerated...low rate of discontinuation⁶

Like other antiarrhythmic drugs, ETHMOZINE can provoke new rhythm disturbances, make existing arrhythmias worse, or worsen congestive heart failure. Its use should be reserved for patients with documented life-threatening ventricular arrhythmias in whom, in the opinion of the physician, the benefits outweigh the risks.



liable, well-tolerated management of life-threatening arrhythmias



ethmozine... the way to reliable, well-tolerated arrhythmia management





Opens the v

Extensively studied in patients at increased risk of sudden cardiac death⁷

1,072 PATIENTS, STUDIED FOR UP TO 7 YEARS— HISTORY INCLUDED:

One or more coexisting cardiac diseases in 93%

67% had coronary artery disease

53% had myocardial infarction (MI)

43% had congestive heart failure (CHF)

Ventricular arrhythmia suppression comparable to quinidine²

Produced a 90% reduction in nonsustained ventricular tachycardia (VT) and abolished VT in 57% of patients.²

Long-term effectiveness documented in VT patients⁸

Significantly suppressed life-threatening ventricular arrhythmias —99% suppression of VT*—during 1-year follow-up.

th proven antiarrhythmic efficacy

Proven by invasive testing of 117 refractory patients⁸

RESULTS OF PROGRAMMED ELECTRICAL STIMULATION* (N = 117)

% of patients noninducible on ETHMOZINE

Sustained VT (N = 75)	25%	
Nonsustained VT (N = 42)		36%

^{*}Adapted from Horowitz, AJC 1990*

Daily dosage range—450 to 1,500 mg; recommended dosage range is 600–900 mg/day

Effective even in presence of LV dysfunction⁵

ETHMOZINE "...appears to be equally effective...irrespective of LV function or history of CHF." 5

In some cases ETHMOZINE may worsen heart failure in patients with underlying heart disease.

ethmozine...
the way to reliable,
well-tolerated arrhythmia
management





Opens the v

Low incidence of proarrhythmia—even in patients with lethal arrhythmia^{3,4}

INCIDENCE	OF PROAR	RHYTHMIA
-----------	----------	----------

Arrhythmia Severity	No. of Patients	No. of Patients with Proarrhythmia (%)
Benign	99	1 (1.0%)
Potentially lethal*	576	21 (3.6%)
Lethal [†]	397	18 (4.5%)
*Nonsustained VT (NSVT) with significant structural heart disease †Sustained VT, ventricular flutter, and ventricular fibrillation; NSVT with hemodynamic symptoms Cumulative Total	1,072	40 (3.7%)

The only antiarrhythmic continuing to be studied in the Cardiac Arrhythmia Suppression Trial (CAST)⁹

At this time, applicability of the CAST results to other populations (patients without recent MI) and to antiarrhythmics other than IC is uncertain. Considering the lack of evidence of improved survival for any antiarrhythmic drug in patients without life-threatening arrhythmias, it is prudent at this time to reserve the use of ETHMOZINE, as well as other antiarrhythmic agents, for patients with life-threatening ventricular arrhythmias.

Please see last page for full prescribing information.

th low incidence of proarrhythmia, CHF, and discontinuation

98% of patients did not experience any drug-related CHF⁵

CHF was related to discontinuation of therapy in only 1% of patients in U.S. studies even though 43% of patients had prior CHF.

No significant effect on LVEF...even in patients with compromised cardiac function^{4,5}

In a study of 156 patients with varying degrees of LV dysfunction, baseline left ventricular ejection fractions (LVEFs) were virtually unchanged after up to 30 days of therapy with ETHMOZINE.

Long-term tolerability documented in CAPS¹⁰... low rate of discontinuation in U.S. trials⁶

Incidence of the most commonly reported side effects, neurologic and G.I., was comparable to placebo over one year in the Cardiac Arrhythmia Pilot Study (CAPS).¹⁰

The three most frequently occurring side effects reported in clinical studies were dizziness (15.1%), nausea (9.6%), and headache (8.0%). Overall, only 9% of patients in short-term U.S. studies discontinued therapy due to side effects. Only nausea (3.2%) and ECG changes (1.6%) led to discontinuation in greater than 1% of patients.

ethmozine...
the way to reliable,
well-tolerated arrhythmia
management





Opens
the way to
reliable,
well-tolerated
management
life-threateni
arrhythmias

Compatible with the drug regimens of most cardiac patients

No clinically significant interactions with cardiovascular agents such as digoxin, warfarin, vasodilators, beta blockers, ACE inhibitors, or calcium channel blockers.

While no significant change in efficacy has been observed, clearance of ETHMOZINE is decreased and plasma levels increased when used concomitantly with cimetidine. ETHMOZINE increases clearance and decreases half-life of the ophylline preparations. Patients receiving ETHMOZINE should be monitored when either of these medications are concomitantly administered.

Contraindicated in patients with pre-existing second- or third-degree AV block, in those with right bundle branch block when associated with left hemiblock (unless a pacemaker is present), or in presence of cardiogenic shock or known hypersensitivity.

Convenient dosing schedule—available in 200-mg, 250-mg, and 300-mg film-coated tablets

Usual dosage is 600–900 mg/day (200–300 mg q8h)—can be adjusted in 150-mg/day increments at 3-day intervals.







250 mg



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Better things for better living

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REFERENCES:

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6217/June, 1990

ETHMOZINE® (moricizine hydrochloride) TABLETS

DESCRIPTION

THMOZINE (moricizine hydrochloride) is an orally active antiarrhythmic drug available for administration in tablets containing 200 mg, 250 mg and 300 mg of moricizine hydrochloride. The chemical name of moricizine hydrochloride is 10-(3-norpholinopropionyl) phenothiazine-2-carbamic acid ethyl ester hydrochloride and the structural formula is represented

Moricizine hydrochloride is a white to tan crystalline powder, freely soluble in water and has a pKa of 6.4 (weak base). ETHMOZINE tablets contain: lactose, microcrystalline cellulose, sodium starch glycolate, magnesium stearate and dyes FD&C Blue 1, D&C Yellow 10 and FD&C Yellow 6 [200 mg tablet]; FD&C Yellow 6 and FD&C Red 40 [250 mg tablet]; FD&C ue 1 [300 mg tablet]).

CLINICAL PHARMACOLOGY

Rechanism of Action
THMOZINE is a Class I antiarrhythmic agent with potent local anesthetic activity and myocardial membrane stabilizing effect. THMOZINE reduces the fast inward current carried by sodium ions.

In isolated dog Purkinje fibers, ETHMOZINE shortens Phase II and III repolarization, resulting in a decreased action potential duration and effective refractory period. A dose-related decrease in the maximum rate of Phase O depolarization (V_{max}) occurs without effect on maximum diastolic potential or action potential amplitude. The sinus node and atrial tissue of the dog are not

Electrophysiology

Electrophysiology leictrophysiology studies in patients with ventricular tachycardia have shown that ETHMOZINE, at daily doses of 750 mg and 900 mg, prolongs atrioventricular conduction. Both AV nodal conduction time (AH interval) and His-Purkinje conduction time HV interval) are prolonged by 10-13% and 21-26%, respectively. The PR interval is prolonged by 16-20% and the QRS by 7-18%. Prolongations of 2-5% in the corrected QT interval result from widening of the QRS interval, but there is shortening of the DT interval, indicating an absence of significant effect on ventricular repolarization. Intra-atrial conduction or atrial effective feractory periods are not consistently affected. In patients without sinus node dysfunction. FIHMOZINE has minal effects on sinus cycle length and sinus node recovery time. These effects may be significant in patients with sinus node dysfunction. on sinus cycle length and sinus inductionary little. The stress see PRECAUTIONS: Electrocardiographic Changes/Conduction Abnormalities).

n patients with impaired left ventricular function, ETHMOZINE has minimal effects on measurements of cardiac performance in patients with impact on the windown function, it involution has minimal effects of interest memory cardiacle periorities such as cardiac index, stroke volume index, pulmonary capillar, wedge pressure, systemic or pulmonary vascular resistance or ejection fraction, either at rest or during exercise. ETHMOZINE is associated with a small, but consistent increase in resting blood pressure and heart rate. Exercise tolerance in patients with ventricular arrhythmias is unaffected. In patients with insitory of congestive heart failure or anging according to patient swift services are functionary of the pressure product at maximal exercise are unchanged during ETHMOZINE administration. Nonetheless, in some cases worsened heart failure in patients with severe underlying heart disease has been attributed to ETHMOZINE

Other Pharmacologic Effects
Although ETHMOZINE is chemically related to the neuroleptic phenothiazines, it has no demonstrated central or peripheral dopaminergic activity in animals. Moreover, in patients on chronic ETHMOZINE, serum prolactin levels did not increase.

Pharmacokinetics/Pharmacodynamics

Pharmacokinetics/Pharmacodynamics
The antiarrhythmic and electrophysiologic effects of ETHMOZINE are not related in time, course, or intensity to plasma morioizine concentrations or to the concentrations of any identified metabolite, all of which have short (2-3 hours) half-lives. Following single doses of ETHMOZINE, there is a prompt prolongation of the PR interval, which becomes normal within 2 hours, consistent with the rapid fall of plasma morioizine. IT interval shortening, however, peaks at about 6 hours and persists for at least 10 hours. Although an effect on VPD rates is seen within 2 hours after dosing, the full effect is seen after 10-14 hours and persists in full, when therapy is terminated, for more than 10 hours, after which the effect decays slowly, and is still substantial at 24 hours. This suggests either an unidentified, active, long half-life metabolite or a structural or functional "deep compartment" with slow entry from, and release to, the plasma. The following description of parent compound pharmaco-timelies is therapiers of uncertaing releases to the plasma. kinetics is therefore of uncertain relevance to clinical actions.

Following oral administration, ETHMOZINE undergoes significant first-past metabolism resulting in an absolute bioavailability.
of approximately 38%, Peak plasma concentrations of ETHMOZINE are usually reached within 0.5-2 hours. Administration 30 minutes after a meal delays the rate of absorption, resulting in lower peak plasma concentrations, but the extent of absorption is not altered. ETHMOZINE plasma levels are proportional to dose over the recommended therapeutic dose range.

The apparent volume of distribution after oral administration is very large (≥ 300 L) and is not significantly related to body weight. ETHMOZINE is approximately 95% bound to human plasma proteins. This binding interaction is independent of ETHMOZINE plasma concentration.

ETHMOZINE undergoes extensive biotransformation. Less than 1% of orally administered ETHMOZINE is excreted unchanged in the urine. There are at least 26 metabolites, but no single metabolite has been found to represent as much as 1% of the administered lose, and as stated above, antiarrhythmic response has relatively slow onset and offset. Two metabolites are pharmacologically active in at least one animal model: moricizine sulfoxide and phenothiazine-2-carbamic acid ethyl ester suffoxide. Each of these metabolites represents a small percentage of the administered dose (< 0.6%), is present in lower concentrations in the plasma than the parent drug, and has a plasma elimination half-life of approximately

ETHMOZINE has been shown to induce its own metabolism. Average ETHMOZINE plasma concentrations in patients decrease with multiple dosing. This decrease in plasma levels of parent drug does not appear to affect clinical outcome for patients receiving chronic ETHMOZINE therapy.

The plasma half-life of ETHMOZINE is 1.5-3.5 hours (most values about 2 hours) following single or multiple oral doses in patients with ventricular ectopy. Approximately 56% of the administered dose is excreted in the feces and 39% is excreted in the urine. Some ETHMOZINE is also recycled through enterohepatic circulation.

CLINICAL ACTIONS

ETHMOZINE at daily doses of 600-900 mg produces a dose-related reduction in the occurrence of frequent premature ventricular depolarizations (VPDs) and reduces the incidence of nonsustained and sustained ventricular tachycardia (VT). In controlled clinical trials, ETHMOZINE has been shown to have antiarrhythmic activity that is generally similar to that of disopyramide, propranolol and pulnidine at the doses studied. In programmed electrical stimulation studies (PES), ETHMOZINE prevented the induction of sustained ventricular tachycardia in approximately 25% of patients. Activity of ETHMOZINE is maintained during long-term use.

ETHMOZINE is effective in treating ventricular arrhythmias in patients with and without organic heart disease. ETHMOZINE may be effective in patients in whom other antiarrhythmic agents are ineffective, not tolerated and/or contraindicated.

Arrhythmia exacerbation or "rebound" is not noted following discontinuation of ETHMOZINE therapy.

INDICATIONS AND USAGE

ETHMOZINE is indicated for the treatment of documented ventricular arrhythmias, such as sustained ventricular tachycardia, that, in the judgement of the physician are life-threatening. Because of the proarrhythmic effects of ETHMOZINE, its use should be reserved for patients in whom, in the opinion of the physician, the benefits of treatment outweigh the risks.

Initiation of ETHMOZINE treatment, as with other antiarrhythmic agents used to treat life-threatening arrhythmias, should be

Antiarrhythmic drugs have not been proven to improve survival in patients with ventricular arrhythmias

CONTRAINDICATIONS

EUNITARINDICATIONS

ETHMOZINE is contraindicated in patients with preexisting second- or third-degree AV block and in patients with right bundle branch block when associated with left hemiblock (bifascicular block) unless a pacemaker is present. ETHMOZINE is also contraindicated in the presence of cardiogenic shock or known hypersensitivity to the drug.

WARMINGS
Mortality
ETHMOZINE was one of three antiarrhythmic drugs included in the National Heart Lung and Blood Institute's
Cardiac Arrhythmia Suppression Trial (CAST), a long-term multicenter, randomized, double-blind study in
patients with asymptomatic nonlife threatening arrhythmias who had a myocardial infarction more than 6
days, but less than 2 years, previously. An excessive mortality or nonfatal cardiac arrest rate was seen in
patients treated with both of the Class IC agents included in the trial, which led to discontinuation of those 2
arms of the trial. The ETHMOZINE and placebo arms of the trial are continuing.

The applicability of the CAST results to other populations (e.g. those without recent myocardial infarction) and to agents other than IC (particularly to ETHMOZINE which, at this time remains in the trial) is uncertain. Considering the known proarrhythmic properties of ETHMOZINE and the lack of evidence of improved survival for any antiarrhythmic for in patients without life-threatening arrhythmias, it is prudent to rever the use of ETHMOZINE, as well as other antiarrhythmic agents, for patients with life-threatening ventricular

Proarrhythmia

Proarrhythmia
Like other antiarrhythmic drugs, ETHMOZINE can provoke new rhythm disturbances or make existing arrhythmias worse.
These proarrhythmic effects can range from an increase in the frequency of VPDs to the development of new or more severe ventricular tachycardia, e.g. tachycardia that is more sustained or more resistant to conversion to sinus rhythm, with potentially fatal consequences. It is often not possible to distinguish a proarrhythmic effect from the patients' underlying rhythm disorder, so that the occurrence rates given below must be considered approximations. Note also that drug-induced arrhythmias can generally be identified only when they occur early after starting the drug and when the rhythm can be identified, usually because the patient is being monitored. It is clear from the NIH-sponsored CAST (Cardiac Arrhythmia Suppression Trial) that some antiarrhythmic drugs can cause increased sudden death mortality, presumably due to new arrhythmias or asystole that do not appear early after treatment but that represent a sustained increased risk.

Domestic premarketing trials included 1072 patients given ETHMOZINE; 397 had baseline lethal arrhythmias (sustained VT Donless plentarising trans induced 1072 patients given or Involving, 397 had obsenine feating an influential sustained VT or VF and nonsustained VT with hemodynamic symptoms) and 576 had obtentially lethal arrhythmias (increased VPDs or NSVT in patients with known structural heart disease, active ischemia, congestive heart failure or an LVEF < 40% and/or Cl < 2.0 1/min/m²). In this population there were 40 (3.7%) identified proarrhythmic events, 26 (2.5%) of which were serious, either fatal (6), new hemodynamically significant sustained VT or VF (4), new sustained VT that was not hemodynamically significant (11) or sustained VT that became syncopal/presyncopal when it had not been before (5).

In general, serious proarrhythmic effects were equally common in patients with more and less severe arrhythmias, 2.596 in the patients with baseline lethal arrhythmias vs. 2.896 in patients with potentially lethal arrhythmias, although the patients with serious effects were more likely to have a history of sustained VT (38% vs. 23%).

Five of the six fatal proarrhythmic events were in patients with baseline lethal arrhythmias; four had prior cardiac arrests. Rates and sevenity of proarrhythmic events were similar in patients given 600-900 mgof ETHMOZINE per day and those given higher doses. Patients with proarrhythmic events were similar in patients given 600-900 mgof ETHMOZINE per day and those given higher doses. Patients with proarrhythmic events were more likely than the overall population to have coronary artery disease (85% vs. 67%), history of acute myocardial infaction (75% vs. 53%), congestive heart failure (60% vs. 43%), and cardiomegaly (55% vs. 33%). All of the six proarrhythmic deaths were in patients with coronary artery disease; 5/6 each had documented acute myocardial infarction, congestive heart failure, and cardiomegaly.

Electrolyte Disturbances

Electrolyte instructions.

Hypokalemia, byperkalemia or hypomagnesemia may alter the effects of Class I antiarrhythmic drugs. Electrolyte imbalances should be corrected before administration of ETHMOZINE.

Sick Sinus Syndrome
ETHMOZINE should be used only with extreme caution in patients with sick sinus syndrome, as it may cause sinus bradycardia, sinus pause or sinus arrest.

PRECAUTIONS

General: Electrocardiographic Changes/Conduction Abnormalities
ETHMOZINE slows AV nodal and intraventricular conduction, producing dose-related increases in the PR and QRS intervals, in clinical trials, the average increase in the PR interval was 12% and the QRS interval was 14%. Although the QTC interval is increased, this is wholly because of QRS prolongation, the JT interval is shortened, indicating the absence of significant slowing of ventricular repolarization. The degree of lengthening of PR and QRS intervals does not predict efficacy.

In controlled clinical trials and in open studies, the overall incidence of delayed ventricular conduction, including new bundle branch block pattern, was approximately 9.4%. In patients without baseline conduction abnormalities, the frequency of second-degree AV block was 0.2% and third-degree AV block did not occur. In patients with baseline conduction abnormalities, the frequencies of second-degree AV block and third-degree AV block were 0.9% and 1.4%, respectively.

ETHMOZINE therapy was discontinued in 1.6% of patients due to electrocardiographic changes (0.6% due to sinus pause or asystole, 0.2% to AV block, 0.2% to junctional rhythm, 0.4% to intraventricular conduction delay, and 0.2% to wide QRS and/ or PR interval).

In patients with preexisting conduction abnormalities, ETHMOZINE therapy should be initiated cautiously. If second- or third-degree AV block occurs, ETHMOZINE therapy should be discontinued unless a ventricular pacemaker is in place. When changing the dose of ETHMOZINE or adding concomitant medications which may also affect cardiac conduction, patients should be monitored electrocardiographically

Patients with significant liver dysfunction have reduced plasma clearance and an increased half-life of ETHMOZINE. Although the precise relationship of ETHMOZINE levels to effect is not clear, patients with hepatic disease should be treated with lower doses and closely monitored for excessive pharmacological effects, including effects on ECG lintense, before dosage adjustment. Patients with severe liver disease should be administered ETHMOZINE with particular care, if at all. (See DOSAGE AND ADMINISTRATION)

Renal Impairment

Renal Impairment
Plasma levels of intact ETHMOZINE are unchanged in hemodialysis patients, but a significant portion (39%) of ETHMOZINE is
metabolized and excreted in the urine. Although no identified active metabolite is known to increase in people with renal
failure, metabolites of unrecognized importance could be affected. For this reason, ETHMOZINE should be administered
cautiously in patients with impaired renal function. Patients with significant renal dysfunction should be started on lower doses
and monitored for excessive pharmacologic effects, including ECG intervals, before dosage adjustment. (See DOSAGE AND
ANAMETERIATION). ADMINISTRATION)

Congestive Heart Failure

Most patients with congestive heart failure have tolerated the recommended ETHMOZINE daily doses without unusual toxicity or change in effect. Pharmacokinetic differences between ETHMOZINE patients with and without congestive heart failure were not apparent (see Hepatic Impairment above). In some cases, worsened heart failure has been attributed to ETHMOZINE. Patients with preexisting heart failure should be monitored carefully when ETHMOZINE is initiated.

Effects on Pacemaker Threshold
The effect of ETHMOZINE on the sensing and pacing thresholds of artificial pacemakers has not been sufficiently studied. In such patients, pacing parameters must be monitored, if ETHMOZINE is used.

Drug InteractionsNo significant changes in serum digoxin levels or pharmacokinetics have been observed in patients or healthy subjects receiving concomitant ETHMOZINE therapy. Concomitant use was associated with additive prolongation of the PR interval, but not with a significant increase in the rate of second- or third-degree AV block.

Concomitant administration of cimetidine resulted in a decrease in ETHMOZINE clearance of 49% and a 1.4 fold increase in plasma levels in healthy subjects. During clinical trials, no significant changes in the efficacy or tolerance of ETHMOZINE have been observed in patients receiving concomitant cimetidine therapy. Patients on cimetidine should have ETHMOZINE have been observed in patients receiving concomitant cimetidine therapy. Patients on cimetidine should have ETHMOZINE have been observed in patients receiving concomitant cimetidine therapy is instituted or discontinued or when the ETHMOZINE dose is changed.

Concomitant administration of beta blocker therapy did not reveal significant changes in overall electrocardiographic intervals in patients. In one controlled study, ETHMOZINE and propranolol administered concomitantly produced a small additive in patients. In one control increase in the PR interval.

Theophylline clearance and plasma half-life were significantly affected by multiple dose ETHMOZINE administration when both conventional and sustained release theophylline were given to healthy subjects (clearance increased 44-66% and plasma half-life decreased 19-33%). Plasma theophylline levels should be monitored when concomitant ETHMOZINE is

Because of possible additive pharmacologic effects, caution is indicated when ETHMOZINE is used with any drug that affects cardiac electrophysiology. Uncontrolled experience in patients indicates no serious adverse interaction during the concomi-tant use of ETHMOZINE and diuretics, vasodilators, antihypertensive drugs, calcium channel blockers, beta blockers, ACE inhibitors, and warfarin, Plasma warfarin levels, warfarin pharmackinetics, and prothrombin times were unaffected during multiple dose ETHMOZINE administration to healthy subjects.

Results from in vitro studies do not suggest alterations in ETHMOZINE plasma protein binding in the presence of other highly

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

in a 24-month mouse study in which ETHMOZINE was administered in the feed at concentrations calculated to provide doses ranging up to 320 mg/kg/day, ovarian tubular aderiomas and granulosa cell tumors were limited in occurrence to ETHMOZINE treated animals. Although the findings were of borderline statistical significance, or not statistically significant, historical control data indicate that both of these tumors are uncommon in the strain of mouse studied.

In a 24-month study in which ETHMOZINE was administered by gavage to rats at doses of 25, 50 and 100 mg/kg/day, Zymbal's Gland Carcinoma was observed in one mild-dose and two high-dose males. This tumor appears to be uncommon in the strain of rast studied. Rats of both sexes also showed a dose-related increase in hepatocellular cholangioma (also described as bile ductile cystadenoma or cystic hyperplasa) along with fatly metamorphosis, possibly due to disruption of hepatic choline utilization for phospholipid biosynthesis. The rat is known to be uniquely sensitive to alteration in choline metabolism.

ETHMOZINE was not mutagenic when assayed for genotoxicity in *in vitro* bacterial (Ames test) and mammalian (Chinese hamster ovary/hypoxanthine-guanine phosphoribosyl transferase and sister chromatid exchange) cell systems or in *in vivo* hamster ovary/hypoxanthine-guanine phosphoribosyl transferase and mammalian systems (rat bone cytogenicity and mouse micronucleus).

A general reproduction and fertility study was conducted in rats at dose levels up to 6.7 times the maximum recommended human dose of 900 mg/day (based upon 50 kg human body weight) and revealed no evidence of impaired male or female fertility.

Pregnancy —Teratogenic Effects:
Pregnancy Category 8
Teratology studies have been performed with ETHMOZINE in rats and in rabbits at doses up to 6.7 and 4.7 times the maximum recommended human daily dose, respectively, and have revealed no evidence of harm to the fetus. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, ETHMOZINE should be used during pregnancy only if clearly needed.

Pregnancy—Nonteratogenic Effects:
In a study in which rats were dosed with ETHMOZINE prior to mating, during mating and throughout gestation and lactation, dose levels 3.4 and 6.7 times the maximum recommended human daily dose produced a dose-related decrease in pup and maternal weight gain, possibly related to a larger litter size. In a study in which dosing was begun on Day 15 of gestation. ETHMOZINE, at a level 6.7 times the maximum recommended human daily dose, produced a retardation in maternal weight gain but no effect on pup growth.

Nursing Mothers
ETHMOZINE is secreted in the milk of laboratory animals and has been reported to be present in human milk. Because of the
potential for serious adverse reactions in nursing infants from ETHMOZINE, a decision should be made whether to
discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
The safety and effectiveness of ETHMOZINE in children less than 18 years of age have not been established.

ADVERSE REACTIONS

The most serious adverse reaction reported for ETHMOZINE is proarrhythmia (see WARNINGS). This occurred in 3.7% of 1072 patients with ventricular arrhythmias who received a wide range of doses under a variety of circumstances.

In addition to discontinuations because of proarrhythmias, in controlled clinical trials and in open studies, adverse reactions led to discontinuation of ETHMOZINE in 7% of 1105 patients with ventricular and supraventricular arrhythmias, including 3.296 due to loaces, 1.696 due to ECG abnormalities (principally conduction defects, sinus pause, junctional rhythm, or AV block), 19% due to congestive heart failure, and 0.3-0.496 due to dizziness, anxiety, drug fever, urinary retention, blurred vision, gastrointestinal upset, rash, and laboratory abnormalities.

The most frequently occurring adverse reactions in the 1072 patients (including all adverse experiences whether or not considered ETHMOZINE-related by the investigator) were dizziness (15.1%), nausea (9.6%), headache (8.0%), failique (5.9%), palpitations (5.8%), and dyspnea (5.7%). Dizziness appears to be related to the size of each dose. In a comparison of 900 mp(day) given at 450 mg b.i.d. or 300 mg t.i.d., more than 20% of patients experienced dizziness on the b.i.d. regimen vs. 12% on the t.i.d. regimen.

Adverse reactions reported by less than 5%, but in 2% or greater of the patients were: sustained ventricular tachycardia, hypesthesia, abdominal pain, dyspepsia, vorniting, sweating, cardiac chest pain, asthenia, nervousness, paresthesia, congestive heart failure, musculoskeletal pain, diarrhea, dry mouth, cardiac death, sleep disorders, and blurred vision.

Adverse reactions infrequently reported (in less than 2% of patients) were:

Cardiovascular hypotension, hypertension, syncope, supraventricular arrhythmias (including atrial fibrillation/flutter), cardiac arrest, bradyoardia, pulmonary embolism, myocardial infarction, vasodilation, cerebrovascular events, this proposibilities.

tremor, anxiety, depression, euphoria, confusion, somnolence, agitation, seizure, coma, abnormal gait. **Nervous System** s, nystagmus, diplopia, speech disorder, akathisia, loss of memory, ataxia, abnormal coordination, dyskinesia,

vertigo, tionitus;

Gentfouthary urinary relention or frequency, dysuria, urinary incontinence, kidney pain, impotence, decreased libido;
Respiratory hyperventilation, apnea, asthma, pharyngitis, cough, sinusitis;
Gastrointestinal anorexia, bitter taste, dysphagia, flatulence, ileus;
Other drug fever, hypothermia, temperature intolerance, eye pain, rash, pruritus, dry skin, urticaria, swelling of the lipsand tongue, periorbital edema.

During ETHMOZINE therapy, two patients developed thrombocytopenia that may have been drug-related. Clinically significant elevations in liver function tests (bilinibin, serum transaminases) and jaundice consistent with hepatitis were rarely reported. Although a cause and effect relationship has not been established, caution is advised in patients who develop unexplained signs of hepatic dysfunction, and consideration should be given to discontinuing therapy.

Three patients developed rechallenge-confirmed drug fever, with one patient experiencing an elevation above 103°F (to 105°F, with rigors). Fevers occurred at about 2 weeks in 2 cases, and after 21 weeks in the third. Fevers resolved within 48 hours of discontinuation of moricizine.

Adverse reactions were generally similar in patients over 65 (n=375) and under 65 (n=697), although discontinuation of therapy for reasons other than proarrhythmia was more common in older patients (13.9% vs. 7.7%). Overall mortality was greater in older patients (9.3% vs. 3.9%), but those were not deaths attributed to treatment and the older patients had more serious underlying heart disease.

The following table compares the most common (occurrence in more than 2% of the patients) noncardiac adverse reactions (i.e., drug-related or of unknown relationship) in controlled clinical trials during the first one to two weeks of therapy with ETHMOZINE, quinidine, placebo, disopyramide, or propranolol in patients with ventricular arrhythmias.

INCIDENCE (%) OF THE MOST COMMON ADVERSE REACTIONS (THERAPY DURATION = 1-14 DAYS)

Adverse	>2 Morio	cizine		>2% Placebo	Q	>2% uinidine	Disc	>5% pyramide		>5% ropranolo
Reactions	No.	%	No.	%	No.	96	No.	%	No.	
Total No. of Patients	1072		618		110		31		24	
Dizziness	121	11.3	33	5.3	8 7	7.3	1 = 1	HARA KA	2	11-50-1
Nausea	74	6.9	18	2.9	7	6.4	3	9.7	-	
Headache	62	5.8	27	4.4	-		-		4	
Pain	41	3.8	31	5.0	6	5.5	2	6.5	-	
Dyspnea	41	3.8	22	3.6	-		-		-	
Hypesthesia	40	3.7	1 =		3	2.7	-		-	
Fatigue	33	3.1	16	2.6	6	5.5	2	6.5	3	22
Vomiting	22	2.1	-		-		1		-	
Dry Mouth	-		-		-		11	35.5	-	
Nervousness	-		-		-		3 2	9.7	2	
Blurred Vision			-		3	2.7	2	6.5	3	
Diarrhea	-		1-		25	22.7	+5		-	
Constipation			-		4		2	6.5		
Somnolence	-		-		7		Y-+		2	
Urinary Retention	4 500		-				4	12.9		

OVERDOSAGE

Deaths have occurred after accidental or intentional overdosages of 2,250 and 10,000 mg of ETHMOZINE, respectively.

Signs, Symptoms and Laboratory Findings Associated with an Overdosage of Drug
Overdosage with ETHMOZINE may produce emesis, lethargy, coma, syncope, hypotension, conduction disturbanc
exacerbation of congestive heart failure, myocardial infarction, sinus arrest, arrhythmias, (including junctional bradycan ventricular tachycardia, ventricular fibrillation and asystole), and respiratory failure.

Lethal Dose in Animals
Oral doses of ETHMOZINE of about 200 mg/kg in dogs, 250 mg/kg in monkeys, 420 mg/kg in mice and 905 mg/kg in rats w
lethal to about one-half of the animals exposed. Death was usually preceded by tremors, convulsions and respirat

Recommended General Treatment Procedures

A specific antidote for ETHMOZINE has not been identified. In the event of overdosage, treatment should be support Patients should be hospitalized and monitored for cardiac, respiratory and CNS changes. Advanced life support systemiculding an intracardiac pacing catheter, should be provided where necessary. Acute overdosage should be treated v appropriate gastric evacuation, and with special care to avoid aspiration. Accidental introduction of ETHMOZINE into the lur of monkeys resulted in rapid arrhythmic death

DOSAGE AND ADMINISTRATION

The dosage of ETHMOZINE must be individualized on the basis of antiarrhythmic response and tolerance. Clinical, card rhythm monitoring, electrocardiogram intervals, exercise testing, and/or programmed electrical stimulation testing may used to guide antiarrhythmic response and dosage adjustment. In general, the patients will be at high risk and should hospitalized for the initiation of therapy (see INDICATIONS AND USAGE).

The usual adult dosage is between 600 and 900 mg per day, given every 8 hours in three equally divided doses. Within 1 range, the dosage can be adjusted as tolerated, in increments of 150 mg/day at 3-day intervals, until the desired effec obtained. Patients with life-threatening arrhythmias who exhibit a beneficial response as judged by objective criteria (MOZINE therapy, the antiarrhythmic effect of ETHMOZINE persists for more than 12 hours, some patients whose arrhythmias are we controlled on a 08H regimen may be given the same total daily dose in a 012H regimen to increase convenience and h assure compliance. When higher doses are used, patients may experience more dizziness and nausea on the Q1 regimen.

Patients with Hepatic Impairment

Patients with hepatic disease should be started at 600 mg/day or lower and monitored closely, including measurement of F intervals, before dosage adjustment

Patients with Renal Impairment

Patients with significant renal dystunction should be started at 600 mg/day or lower and monitored closely, includi measurement of ECG intervals, before dosage adjustment.

Transfer to ETHMOZINE

Recommendations for transferring patients from another antiarrhythmic to ETHMOZINE can be given based on theoreti considerations. Previous antiarrhythmic therapy should be withdrawn for 1-2 plasma half-lives before starting ETHMOZINE the recommended dosages. In patients in whom withdrawal of a previous antiarrhythmic is likely to produce life-threateni arrhythmias, hospitalization is recommended.

Transferred From	Start ETHMOZINE
Quinidine, Disopyramide	6-12 hours after last dose
Procainamide	3-6 hours after last dose
Encainide, Propafenone, Tocainide, or Mexiletine	8-12 hours after last dose
Flecainide	12-24 hours after last dose

HOW SUPPLIED

HMOZINE (moricizine hydrochloride) is available as oval, convex, film-coated tablets as follows:

200 mg (light green):	Bottles of 100 (NDC 0056-0061-70) Hospital Unit Dose Carton of 100 (NDC 0056-0061-75)
250 mg (light orange):	Bottles of 100 (NDC 0056-0062-70) Hospital Unit Dose Carton of 100 (NDC 0056-0062-75)
300 mg (light blue):	Bottles of 100 (NDC 0056-0064-70) Hospital Unit Dose Carton of 100 (NDC 0056-0064-75)

Store at controlled room temperature (59°-86°F, 15°-30°C) in a tightly-closed, light-resistant container. Keep in carton ur dispensed. Protect from tight.

Du Pont Pharmaceuticals E.I. du Pont de Nemours & Co. Wilmington, Delaware 19898

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Effects of Two Types of Fish Oil Supplements on Serum Lipids and Plasma Phospholipid Fatty Acids in Coronary Artery Disease

Gregg J. Reis, MD, David I. Silverman, MD, Theresa M. Boucher, RN, Mary Ellen Sipperly, RN, Gary L. Horowitz, MD, Frank M. Sacks, MD, and Richard C. Pasternak, MD

Fish oil has consistently been shown to lower triglyceride levels, but its effects on low-density lipoprotein (LDL) cholesterol remain controversial. The current study compares the long-term effects of 2 different fish oil preparations (ethyl ester and triglyceride) versus olive oil in patients with coronary artery disease. Eighty-nine subjects were randomly assigned to receive capsules containing 6 g/day (triglyceride group) or 7 g/day (ethyl ester group) of n-3 fatty acids, or capsules containing 12 g/day of olive oil for 6 months. Mean triglyceride levels decreased by 28% in the ester and 32% in the triglyceride fish oil groups (p <0.05 for both). LDL cholesterol levels increased by 3% (difference not significant) in the ester and 12% (p <0.05) in the triglyceride fish oil groups; in hypertriglyceridemic subjects the increase was 23% (p < 0.01) and 14% (difference not significant), respectively. Plasma phospholipid fatty acid analysis showed a fivefold increase in eicosapentaenoic acid levels in both fish oil groups (p <0.001), and a long-term decrease in arachidonic acid levels (p <0.001). Achieved eicosapentaenoic acid level correlated with the degree of increase in LDL cholesterol (r = 0.38, p < 0.05). These data suggest that fish oil administration is associated with an increase in LDL cholesterol levels in a diverse group of patients with coronary artery disease; this change appears to be correlated with n-3 fatty acid absorption. The impact of this increase in LDL is unknown, but should be considered as potentially adverse.

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From the Charles A. Dana Research Institute and the Harvard-Thorndike Laboratories of the Cardiovascular Division, Beth Israel Hospital, and the Channing Laboratory, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts. This study was supported in part by Grant RR-01032 from the General Clinical Research Centers Program of the Division of Research Resources, National Institutes of Health, Bethesda, Maryland. Dr Sacks is a recipient of an Established Investigator Award from the American Heart Association, Dallas, Texas. The Warner-Lambert Corporation, Morris Plains, New Jersey, and Pharmacaps, Inc., Elizabeth, New Jersey, provided fish oil and placebo capsules for the trial. Manuscript received April 20, 1990; revised manuscript received and accepted July 5, 1990.

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espite extensive study, controversy exists regarding the potential efficacy of fish oil supplements for the prevention or treatment of atherosclerosis. No controlled trials of fish oil for this indication have been performed to date in humans; studies in patients undergoing coronary angioplasty have yielded conflicting results^{1,2} for the prevention of recurrent coronary artery stenosis (restenosis). Furthermore, the mechanism by which fish oil is potentially antiatherosclerotic remains unresolved.3 An important question concerns the effect of fish oil supplements on plasma lipid levels. Whereas consistent reductions in plasma triglyceride and very low density lipoprotein (VLDL) cholesterol levels have been reported, effects on low-density lipoprotein (LDL) cholesterol levels have been variable.4-10

Levels of n-3 fatty acids during fish oil supplementation have been measured in various tissues, including plasma, 11-13 platelet membranes 11,12 and erythrocyte membranes.¹³ Marked increases in eicosapentaenoic (20:5, n-3) and docosahexaenoic (22:6, n-3) acids occur, as do decreases in levels of arachidonic acid (20:4, n-6); these changes may account for the inhibition of platelet aggregation that occurs in patients receiving fish oil. 11-15 Although the lipid and fatty acid effects of fish oil are dose-dependent, the relation between changes in plasma or membrane fatty acid composition and serum lipids is largely unexplored.

Most studies of fish oil supplementation have been relatively short-term (≤1 month), and have used as subjects normal volunteers or patients with hypertriglyceridemia. Fish oil has been increasingly used for treatment of patients with other types of hyperlipidemias or atherosclerosis. 16 The current study tests the effects on serum lipid and plasma phospholipid fatty acid levels of long-term fish oil supplementation in patients with coronary artery disease and heterogenous baseline lipid levels.

METHODS

Study design: This study was conducted as part of a larger trial of fish oil in the prevention of restenosis after coronary angioplasty.2 Eighty-nine patients undergoing coronary angioplasty at the Beth Israel Hospital were enrolled in this portion of the trial. Patients with a history of recent significant bleeding were excluded. There were 13 patients taking lipid-lowering medications at the onset of the study; these patients were not excluded, but were maintained on the same medication for the study duration.

All aspects of the protocol were approved by the hospital's Committee on Clinical Investigations. Informed consent was obtained from all patients, who were then randomly assigned to receive 1 of 3 preparations: (1) ethyl esters of fatty acids extracted from fish oil (Super-EPA, Pharmacaps Corporation, Elizabeth, New Jersey); (2) a purified fish oil containing the fatty acids in triglyceride (Promega, Parke-Davis Division of Warner-Lambert Corporation, Morris Plains, New Jersey); or (3) identical capsules containing olive oil. The study was conducted in a double-blind fashion. Of the 89 patients, 32 were randomly assigned to the ethyl ester fish oil, 36 to the triglyceride fish oil and 21 to olive oil; the lower number in the latter group is partly a consequence of the design of the angioplasty trial, during a pilot phase of which patients were randomized to receive 1 of the fish oil formulations without randomization to a control group (28 patients). The remaining 61 patients were randomized concurrently.

Each patient took twelve 1-g capsules/day for a period of 6 months. The SuperEPA capsules supplied 7.0 g/day of n-3 fatty acids (3.7 g eicosapentaeonoic, 2.5 g docosahexaenoic, 0.8 g other); the Promega supplied 6.0 g/day n-3 fatty acids (3.4 g eicosapentaenoic, 1.4 g docosahexaenoic, 1.2 g other). The daily dosage of both fish oil and olive oil capsules contained 12 g of total fat, 108 calories and <12 mg of cholesterol. Medication compliance was determined by pill count at the 6-month follow-up. Patients received general dietary counseling during their hospital admission in accordance with American Heart Association Phase I or National Cholesterol Education Program Step I diets. Dietary compliance was assessed using standardized semiquantitative questionnaires.

Fasting blood samples were obtained at baseline, at the time of angioplasty before systemic heparinization $(5.9 \pm 1.3 \text{ days after initiation of treatment})$ and at 6 months. Approximately 10 ml of blood was collected in

a serum separator tube (Corvac, Sherwood Medical, St. Louis, Missouri) and centrifuged at 1,000 × g. In a subset of 42 patients, an additional 10 ml of blood was drawn into tubes containing 1 mg/ml of ethylenediaminetetraacetic acid, and plasma separated by centrifugation. If not analyzed immediately, samples were stored at -70°C.

Lipid and lipoprotein analysis: Serum lipids were measured by the clinical chemistry laboratory of the Beth Israel Hospital, using a COBAS-BIO centrifugal analyzer (Roche Diagnostic Systems, Nutley, New Jersey). Cholesterol and triglycerides were measured using a standard enzymatic assay (Abbott Laboratories, North Chicago, Illinois). High-density lipoprotein (HDL) cholesterol was measured simultaneously after treatment of serum with magnesium phosphotungstate (Sigma Diagnostics, St. Louis, Missouri). Typical interassay coefficients of variation for these assays were: cholesterol, 1.1% at 246 mg/dl and 2.1% at 139 mg/dl; HDL cholesterol, 5.8% at 26 mg/dl; and triglycerides, 3.5% at 185 mg/dl and 5.5% at 100 mg/dl. LDL cholesterol was calculated using the formula LDL cholesterol = total cholesterol - HDL cholesterol - triglyceride/5, when triglyceride is ≤400 mg/dl. In 3 patients with triglyceride levels >400 mg/dl, LDL was not calculated, and these patients were not included in analysis of LDL results.

Fatty acid analysis: Total lipid extractions were performed on a 100 µliter aliquot of plasma using a 3:2 hexane:isopropanol mixture.¹⁷ The solvent was evaporated, and the lipids redissolved and applied to a thin layer chromatography plate. The plasma phospholipid fraction was then separated using an 83.3% petroleum ether/14.7% ethyl ether/1.9% glacial acetic acid mixture as the solvent. Phospholipids were removed from the plate, esterified in the presence of methanol and acetyl chloride¹⁸ and evaporated to dryness. The fatty acid methyl esters were dissolved in isooctane, and analyzed by gas-liquid chromatography (Hewlett-Packard model 5980) using a 60 × 0.32 meter, 90% bis-cyano-

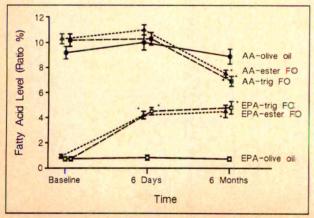


FIGURE 1. Response of plasma phospholipid fatty acid levels to fish oil or olive oil treatment. Levels are percentages of total fatty acids, mean \pm standard error of the mean. AA = arachidonic acid; EPA = eicosapentaenoic acid; Ester FO = ethyl ester fish oil; Trig FO = triglyceride fish oil. * p <0.001 vs base-

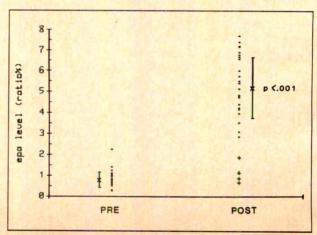


FIGURE 2. Eicosapentaenoic acid (epa) levels before (PRE) and after (POST) 6 months of fish oil treatment. Crosses represent patients who were known to have discontinued therapy before measurement. Mean ± standard deviation is shown for patients compliant with therapy.

TABLE I Effects of Fish Oil Supplementation on Serum Lipids

	Total Chol.	HDL Chol.	Triglyceride	LDL Chol.
Ethyl ester Fo	O(n = 32)			
Baseline	215 ± 51	41 ± 14	218 ± 248	137 ± 39
6 months	210 ± 43	43 ± 17	156 ± 230*	141 ± 39
Triglyceride F	FO(n = 36)			
Baseline	217 ± 38	38 ± 12	202 ± 88	138 ± 32
6 months	224 ± 32	43 ± 15	137 ± 61*	155 ± 29*
Olive oil (n =	21)			
Baseline	214 ± 46	39 ± 14	200 ± 159	141 ± 43
6 months	207 ± 43	41 ± 13	190 ± 164	137 ± 42

* p <0.05 versus olive oil group.

Values are mean ± standard deviation in mg/deciliter.

Chol. = cholesterol; FO = fish oil; HDL = high-density lipoprotein; LDL = low-density

propyl, 10% phenylcyanopropyl siloxane phase column (Restek, RTX 2330, Bellefonte, Pennsylvania). Retention times and response factors for each fatty acid were determined using authentic standards. Total and individual n-3 fatty acid levels are reported as percentages of total plasma phospholipid fatty acids. Samples were adequate for analysis in 38 of the 42 patients in which they were obtained.

Statistical analysis: Comparisons of changes in lipid levels between treatment groups were done using analysis of variance for repeated measures. Changes in fatty acid levels were compared using Student's t test for paired observations. Where appropriate, multiple logistic regression analyses were performed using the Prophet system, a national computer resource sponsored by the Division of Research Resources of the National Institutes of Health. Values were considered significant at p < 0.05.

RESULTS

Fatty acid effects: Baseline levels of n-3 and arachidonic acids in plasma phospholipids were similar in all groups. Eicosapentaenoate levels increased fivefold from baseline to the time of first repeat measurement (mean, 5.9 ± 1.3 days of treatment) in the fish oil-treated groups; this increase was sustained after 6 months of treatment (Figure 1). Similar changes were noted in levels of other n-3 fatty acids (not shown). Arachidonate levels did not change by 5.9 ± 1.3 days, but decreased significantly at 6 months in both fish oil groups. The eicosapentaenoic/arachidonic acid ratio increased from 0.08 ± 0.04 at baseline, to 0.43 ± 0.16 at 6 days, and 0.69 ± 0.36 at 6 months (p < 0.001). Despite excellent compliance with study medication (92 ± 19%, no difference among groups), there was variability in individual patient response (Figure 2). If the 4 patients who discontinued fish oil 2 to 14 days before 6-month followup are excluded from analysis, the levels of fatty acids at follow-up were: eicosapentaenoic, 5.2 ± 1.5%, docosahexaenoic, 6.1 \pm 2.2%, total n-3, 12.6 \pm 3.2%, and arachidonic, 7.1 ± 1.3%. All values are changed from baseline and significantly different from the olive oil group (p <0.001). Interestingly, among the 4 patients who discontinued fish oil early, n-3 levels were identical to olive oil-treated patients, but arachidonic acid levels remained lower, suggesting that changes in arachidonic

TABLE II Effect of Baseline Triglyceride on Response to Fish Oil Therapy

	Baseline Trig. (mg/dl)	No.	Change Trig. (%)	Change LDL Chol. (%)
Ethyl ester	<150	12	-10	-4
fish oil	150-250	14	-32	+6
	>250	5	-49*	+23*
Triglyceride	<150	15	-23	+14
fish oil	150-250	9	-31	+13
	>250	11	-34*	+14

p < 0.01 for association of lipid effect of fish oil with baseline triglyceride Percentages represent change in lipid value from baseline Chol. = cholesterol; Trig. = triglyceride.

acid levels induced by fish oil lag behind n-3 levels both in onset and in their return to baseline.

Despite the slightly higher daily dose of n-3 fatty acids in the ethyl ester group (7 vs 6 g), plasma n-3 levels were slightly (although not significantly) lower in this group than in the triglyceride group, possibly reflecting poorer absorption of the ethyl ester, as has been observed in other studies. 19 There were no significant changes in any fatty acid levels including oleic acid (18:1) in the olive oil group.

Serum lipids: The effects of the 2 types of fish oil supplementation and olive oil on serum lipids are listed in Table I. As expected, triglyceride levels decreased significantly in both fish oil groups. Calculated LDL cholesterol levels increased by 12% in the group treated with the triglyceride fish oil preparation; there was no significant change in the ethyl ester-treated group. There were no changes in serum lipid levels in the olive oil-treated group.

The increase in plasma phospholipid eicosapentaenoate levels correlated with the increase in LDL cholesterol. Fish oil-treated patients in whom eicosapentaenoic acid comprised >4.5% of plasma fatty acids at followup (n = 24) had a mean increase in LDL cholesterol of 30 ± 28 mg/dl; those with lower achieved levels (<4.5%, n = 14) had only a 5 \pm 22 mg/dl increase (p <0.05). Multiple logistic regression analysis revealed eicosapentaenoate level to be independently associated

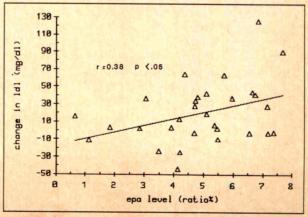


FIGURE 3. Effect of achieved eicosapentaenoic acid (epa) level on change in LDL cholesterol with fish oil therapy. A weak but significant association is present.

with the change in LDL cholesterol (r = 0.38, p < 0.05), even after accounting for the association with baseline triglycerides. This suggests a weak dose-response relation (Figure 3). There were no correlations between n-3 levels and changes in triglycerides.

Baseline triglyceride levels influenced the response of serum lipids to fish oil therapy (Table II). Hypertriglyceridemic patients had the greatest decrease in serum triglycerides with fish oil therapy, both absolutely and on a percentage basis. Although baseline triglyceride levels influenced changes in LDL cholesterol in the ethyl ester group, there was no apparent effect in the triglyceride fish oil group.

DISCUSSION

In this study of 89 patients with coronary artery disease, fish oil supplementation with either a triglyceride or ethyl ester formulation produced significant decreases in serum triglyceride levels and increases in LDL cholesterol levels. Patients achieving high plasma n-3 levels had the greatest increases in LDL cholesterol.

Fish oil decreases VLDL cholesterol and plasma triglycerides primarily by decreasing hepatic production of VLDL,²⁰ probably by inhibiting the enzyme (acyl-coenzyme A:1,2-diacylglycerol acyltransferase) catalyzing the final step in triglyceride synthesis.²¹ The effects of fish oil supplementation of LDL cholesterol levels have been variable, 4-10 and the mechanism less clearly elucidated. Fish oil, in addition to decreasing the production of VLDL, causes production of smaller, less triglyceride-rich VLDL,8 which has been shown to be more easily converted to LDL.22

Therefore, particularly in patients with hypertriglyceridemia, the net result of fish oil administration may be a paradoxical increase in LDL levels.8-10 In the present study, increases in LDL cholesterol levels occurred even in patients with normal triglyceride levels. A similar finding was noted by Dehmer et all in a diverse population of patients undergoing coronary angioplasty. While fish oil supplements may be administered to hypertriglyceridemic patients in an attempt to normalize lipid levels, the suggestion of a direct antiatherosclerotic effect of fish oils in population studies^{23,24} or animal experiments25 has led to increasing use of fish oil by clinicians for other indications. 16 In addition, aggressive marketing efforts have been undertaken to promote sales of over-the-counter fish oil preparations.

Although LDL cholesterol increased primarily in patients treated with the triglyceride fish oil, multiple regression analysis indicates that this was primarily a function of higher n-3 fatty acid levels. Unlike max-EPA, neither Promega or SuperEPA contain significant amounts of cholesterol or saturated fat, so it is likely that the n-3 fatty acids themselves are responsible for the observed changes in serum lipids. In analyzing prior studies for the effects of fish oil on lipids, it is important to distinguish between those that substituted fish or fish oils for other dietary components4-6,26 and those that have added fish oil supplements but left diet unchanged. 1,7-10 Studies in which fish or fish oil was substituted have generally demonstrated decreases in to-

tal and LDL cholesterol, probably due to a reduction in saturated fat intake.²⁷ The studies of "pure" fish oil supplementation have more consistently shown increases in LDL cholesterol, although very high doses (up to 25 g/day of n-3 fatty acids) have resulted in decreases in some patients with type IIb hyperlipidemia.6 The current study shows the increase in LDL to be correlated with achieved plasma n-3 levels.

An additional finding in the present study was that the decrease in plasma phospholipid arachidonic acid levels was delayed. Studies of the effect of fish oil on platelet function have suggested that there is a progressive inhibition over several weeks. 13,28 It is possible that the gradual decrease in plasma (and membrane) arachidonic acid levels is primarily responsible for platelet inhibition, as this is the substrate for thromboxane-A2, levels of which decrease with fish oil administration. 13,28,29

Study limitations: The current study has 3 important limitations. First, fatty acid levels were measured in plasma, not platelet membranes. However, fatty acid changes in plasma phospholipids parallel those in platelet membranes, with a faster onset and washout.¹⁷ Second, LDL cholesterol levels were calculated rather than measured. A subset of patients did have LDL separated by ultracentrifugation; cholesterol measurements in this group confirmed the increase in calculated LDL. Third, no definite conclusions can be drawn from this study regarding changes in atherosclerosis risk in patients receiving fish oil. It should be noted, however, that the highly unsaturated n-3 fatty acids are more subject to oxidation than other fatty acids, a factor that may increase the atherogenicity of LDL particles containing n-3 fatty acids.

Acknowledgment: We are indebted to Gina McCormack, BS, for facilitating serum lipid analyses, to Donald S. Baim, MD, and Carolyn McCabe, BS, for invaluable advice and technical assistance, and to Carol Ann Centauro and Jill Jarvis for secretarial support.

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Predictive Value of Lipoprotein (a) and Other Serum Lipoproteins in the Angiographic Diagnosis of Coronary Artery Disease

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To determine the relation among lipids in predicting coronary artery disease (CAD), 213 patients undergoing diagnostic angiography for suspected CAD were prospectively studied. Twenty-one patients had normal coronary arteries and 192 had CAD in 1 to 3 arteries at arteriography with measurements obtained with digital calipers. Lipoproteins were measured and lipoprotein (a) [Lp(a)] was also assayed in a subset of 98 patients with CAD. Statistical analysis was performed using uni- and multivariate techniques to test the association among age, gender, systemic hypertension, diabetes mellitus, cigarette smoking, family history, total cholesterol. triglycerides, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, very low density lipoprotein cholesterol, apolipoproteins (apo) A-I and apo B, ratio of apo A-I to apo B, and ratio of HDL cholesterol to total cholesterol, to Lp(a) and to CAD. All factors except gender, systemic hypertension, diabetes mellitus and cigarette smoking were univariate predictors of CAD. Multivariate predictors were, in decreasing order of significance, family history, age, HDL/total cholesterol ratio and apo B. When Lp(a) was included, multivariate predictors were age, family history, apo B and Lp(a), in that order. Lipid parameters alone showed that the HDL/total cholesterol ratio and that Lp(a) provide the best predictive tests for the detection of CAD in this referral population and may ultimately become important screening tests for CAD.

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revious studies of the association among various lipoprotein classes and the angiographic verification of coronary artery disease (CAD) have shown similar but sometimes slightly disparate results, especially when relating the relative importance of the ratio of high-density lipoprotein (HDL) cholesterol to total cholesterol versus apolipoprotein (apo) A-I or apo B.1-4 However, these studies all used visual grading of coronary stenoses, which is known to be error-prone. To determine if objective evidence of CAD, as determined by angiography with percent stenosis measured with digital calipers,5 could be predicted by serum lipids, a new class of lipoproteins, namely lipoprotein (a) [Lp(a)], which has recently attracted attention as a risk factor for CAD, were measured.^{6,7} Lp(a) apolipoproteins consist of apo B and apolipoprotein (a), a protein having a structure similar to plasminogen,8 which binds to fibrin,9 and which has been localized in human atherosclerotic plaques. 10 Epidemiologic studies have shown a correlation of Lp(a) with clinical CAD, whereas angiographic studies¹¹ have shown an association of Lp(a) with the occurrence of vein graft stenoses after coronary artery bypass grafting. 12

METHODS

Patients: The study population consisted of 213 patients undergoing diagnostic coronary angiography for suspected CAD at Emory University Hospital in Atlanta, Georgia. Patients from group A were classified in subgroups with either normal coronary arteries or with 1-, 2- and 3-vessel CAD. A significant stenosis was defined as ≥50% narrowing of the transluminal diameter in the left anterior descending, the left circumflex or the right coronary artery. There were 149 men with an average age 57 ± 19 years (mean \pm standard deviation) and 69 women (mean age 64 ± 18) in group A and 68 men (mean age 55 ± 17) and 20 women (mean age 63± 18) in group B. Blacks were excluded from group B because blacks as a group have much higher Lp(a) levels than do whites. 13

Cardiac catheterization and coronary angiography: Selective coronary angiography was performed in patients after a 12-hour fast. To visualize the entire coronary circulation, repeated injections with 4 to 8 ml of either meglumine diatrizoate or iopamidol were performed. Multiple views, including anteroposterior, right and left anterior oblique, with various cranial and caudal angulations, were recorded on 35-mm cineangio-

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TABLE I Demographic Characteristics CAD 0 0 193 No. of pts 21 13 57 (10) 62 (9) 54(10) 63(10) Age (mean) Gender (% male) 67 70 69 66 Positive family history of 24 48 38 53 CAD (%) Diabetes mellitus (%) 10 22 20 16 History of hypertension (%) 33 52 31 55 Cigarette smoking (%) 52 53 61 45 CAD = coronary artery disease; 0 = normal; + = diseased. Values are mean \pm standard deviation.

TABLE II Mean (± SD) Serum Lipids, Lipopro	otein and
Apolipoproteins in Group A	

NAME OF THE OWNER OWNER OF THE OWNER			p Value
CAD	0	+	
No. of pts.	21	193	
Cholesterol (mg/dl)	189 (38)	214 (46)	0.014
Triglycerides (mg/dl)	115 (50)	169 (104)	0.016
HDL-C (mg/dl)	54 (18)	42 (12)	< 0.001
LDL-C (mg/dl)	111 (33)	138 (40)	0.002
VLDL-C (mg/dl)	23 (10)	34(21)	0.016
HDL-C/cholesterol	0.29 (0.10)	0.20 (0.06)	< 0.001
Apo A-I (mg/dl)	117 (33)	101 (27)	0.013
Apo B (mg/dl)	96 (24)	117 (25)	< 0.001
Apo A-I/apo B	1.27 (0.40)	0.91 (0.34)	<0.0001

CAD = coronary artery disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; SD = standard deviation; VLDL-C = very low density lipoprotein cholesterol; 0 = normal; + = diseased.

graphic film at a rate of 30 frames/s. A 5- to 9-inch image intensifier was used as necessary to display the appropriate anatomy. The cine films were projected on Siemens flat, front-viewing projector, and the stenoses were measured with a programmable digital electronic caliper system (Sandhill®) by an observer blinded to the results of the serum analyses. Coronary angiograms were classified on the basis of 0 (absolutely normal) or as ≥50% diameter stenosis in any of 3 epicardial arteries.

Plasma lipid and lipoprotein determinations: All patients were sampled after a 12-hour fast at the time of arteriotomy before systemic heparinization. Serum was obtained by centrifugation of clotted specimen within 30 minutes. Serum specimens were aliquoted into multiple fractions that were frozen at -80°C until analyzed. Total cholesterol and triglyceride levels were determined enzymatically. The procedures were standardized according to the guidelines set by the Lipid Research Clinic Program.¹⁴ There was an intra- and interassay coefficient of variation (CV) of less than 3.0 and 3.5%, respectively, and an accuracy within 5% of the value for a standard cholesterol analysis (Centers for Disease Control, Atlanta, Georgia). Triglyceride levels were determined with inter- and intraassay CVs of 6.2 and 5.1%, respectively. HDL cholesterol was determined enzymatically in the supernates after precipitation of lowdensity lipoprotein (LDL) and very low density lipoprotein with 4% phosphotungstic acid. For HDL cholesterol the inter- and intraassay CVs were 4.5 and 3.6%,

TABLE III Mean (± SD) Serum Lipids, Lipoprotein and Apolipoproteins in Group B

			p Value
CAD	0	+	
No. of pts.	13	85	
Cholesterol (mg/dl)	174 (38)	214 (46)	0.014
Triglycerides (mg/dl)	108 (40)	170 (101)	0.016
HDL-C (mg/dl)	50 (19)	44 (13)	< 0.001
LDL-C (mg/dl)	111 (33)	138 (40)	0.002
VLDL-C (mg/dl)	22 (9)	34 (20)	0.003
HDL-C/cholesterol	0.30 (0.11)	0.21 (0.06)	< 0.001
Apo A-I (mg/dl)	107 (37)	105 (21)	NS
Apo B (mg/dl)	96 (24)	115 (23)	< 0.002
Apo A-I/apo B	1.24 (0.48)	0.95 (0.23)	< 0.0001
Lp (a) (mg/dl)	6.4 (5.6)	16.9 (16.2)	<0.009

NS = difference not significant; other abbreviations as in Table II.

respectively. The values of LDL cholesterol were calculated using the Friedenwald formula.15 Apo A-I and apo B were determined by radioimmunoassay (Ventrex Laboratories, Inc., Portland, Maine). 16 Ten serum samples from normal subjects were assayed in triplicate, with inter- and intraassay CVs of 5.8 and 4.2% found, respectively, for 8 independent observations. Lp(a) was measured with a commercially available noncompetitive enzyme-linked immunosorbent assay (ELISA) (Tint-Elize® Lp(a), Biopool AB, Umea, Sweden). 17 Within assay, variation at Lp(a) concentrations of 10 and 40 mg/dl was 6.6 and 2.3%, respectively (n = 16). Between assays, variation at the same concentrations was 7.7 and 2.7%, respectively. Human plasminogen crossreacted by 0.5% at concentrations of 100 mg/dl of plasminogen in undiluted samples.

Statistical procedures: Analyses were made with the aid of BMDP statistical programs. 18 Of the continuous variables examined, only Lp(a) showed a skewed distribution. Data was compared using a 1-way analysis of variance. A Mann-Whitney test was used to compare Lp(a) between groups. The Duncan new multiple range test was used to identify differences among the groups when the overall statistic F was significant. Multivariate analysis was done with stepwise logistic regression.

RESULTS

Demographic data on the entire population (n = 213) of patients in our study are listed in Table I. Data include the number of patients with and without CAD, their mean age and gender, and the percentage with a positive family history for CAD, a history of diabetes mellitus, systemic hypertension and cigarette smoking. Half of the patients with CAD had a positive family history for heart disease and hypertension compared with one-third of patients without CAD. One-fourth of patients with CAD had diabetes mellitus compared with one-tenth for those without CAD. In all, there were significant differences among patients with and without CAD for the percentage with positive family history, diabetes mellitus and systemic hypertension. No significant difference was found for the percentage of smok-

TABLE IV Mean (± SD) Serum Lipid, Lipoprotein and Apolipoprotein Distribution According to the Number of Diseased Vessels

	Groups			
Variable	Control	Single-	Double-	Triple-Vessel
	(n = 21)	(n = 36)	(n = 79)	(n = 64)
Cholesterol (mg/dl)	192 (40)	198 (60)	215 (32)*	227 (48)*
HDL-C (mg/dl)	56 (15)*	46 (14.1)*	44 (13.3)*	43 (11.3)*
LDL-C (mg/dl)	112 (35)	129 (39)*	134 (33)*	145 (41.7)*
LDL-C/HDL-C	2.2(0.9)*	2.6 (1.3)*	3.3 (1.3)*	3.5 (1.2)*
Apo A-I (mg/dl)	101 (22)	96 (15.2)	88 (17)*	80 (20)*
Apo B (mg/dl)	88 (22)	94.8 (26.5)*	114.1 (19)*	122 (17)*
Apo A-I/apo B	1.23(0.5)	1.1 (0.4)	0.79 (0.2)*	0.66 (0.18)*

^{*} Significantly different from controls. Duncan's multiple range test for variables. Abbreviations as in Table II.

Tables II and III list the mean values and standard deviations for plasma lipids, lipoproteins and apolipoproteins, as well as the ratios of HDL/total cholesterol and apo A-I/apo B in patients with and without CAD. As determined by analysis of variance, mean levels of total cholesterol, triglycerides, LDL cholesterol and apo B were significantly higher in patients with CAD than in those without. HDL cholesterol, apo A-I, the ratios of HDL/total cholesterol and apo A-I/apo B were all significantly lower in patients with CAD. Lp(a) had significantly higher mean values in patients with CAD compared to those without, 16.9 ± 16.2 and 6.4 ± 5.6 mg/dl, respectively.

Table IV lists results from Duncan's multiple range test for variables after all patients were grouped according to the number of diseased vessels. Variables included total, LDL and HDL cholesterol, the ratio of LDL/ HDL cholesterol, apo A-I, apo B and the ratio of apo A-I/apo B. The values from the group with 0 vessel CAD were significantly different (p <0.05) from the values for the groups with 1-, 2- and 3-vessel CAD for LDL and HDL cholesterol and for the ratio of LDL/ HDL cholesterol. In addition, the values for the groups with 1-, 2- and 3-vessel CAD were similar in each instance and in each instance there was no statistically significant difference among them. For total cholesterol, apo A-I, apo B and the ratio of apo A-I/apo B the values for the group with 0 and 1-vessel CAD were not significantly different among themselves, although they were significantly different from the groups with 2 and 3 narrowed arteries. In addition, the values for the group with 2 and 3 diseased vessels were similar.

Figure 1 shows the distribution of Lp(a) according to the number of diseased vessels. Values for controls were significantly different from groups with 1, 2 and 3 vessels with CAD, which were all similar among themselves.

Multivariate analysis, using those demographic and lipid parameters that were significantly different between patients with CAD and control subjects (Tables I, II and III), showed that independent predictors of the presence of angiographic CAD in group A were, in descending order: family history, age, the ratio of HDL/ total cholesterol and apo B. In group B independent predictors were: age, apo B, family history and Lp(a).

Table V compares serum lipids, lipoproteins and apolipoproteins in patients with no demographic risks for CAD. The data show a tendency for increasing LDL cholesterol, apo B and Lp(a) in control subjects and in patients with CAD, respectively. A tendency for

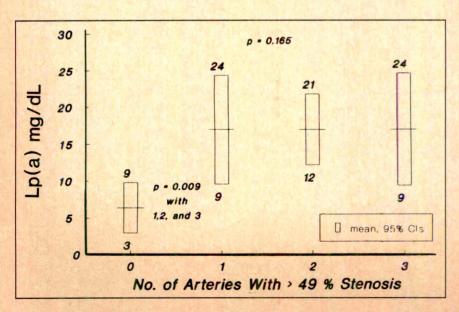


FIGURE 1. Serum lipoprotein Lp(a) levels in patients grouped according to the number of diseased vessels. Cls = 95% confidence intervals.

TABLE V Comparison Between Serum Lipids in CAD Groups with Negative Demographic Risk Factors HDI-C LDL-C Apo A-I/ Lp(a) Triglycerides Total Apo A-I Apo B Apo B (mg/dl) Cholesterol (mg/dl) (mg/dl) (mg/dl) 12 12 12 12 No. of pts 12 12 12 130 (45) 36 (10) 134 (35) 94 (20) 111 (20) 1(0) 14(12) With CAD (mean) 198 (36) 8 8 8 8 8 No. of pts 8 Without CAD (mean) 201 (28) 130 (47) 47 (15) 124(27) 103 (30) 98 (13) 1.1 (0.36) 4(2) Values are mean ± standard deviation.

decreasing HDL cholesterol, apo A-I, and the apo A-I/ apo B ratio was observed in control subjects and in patients with CAD, respectively. Multivariate analysis of the parameters (Table V) showed that the ratio of HDL/total cholesterol and the Lp(a) were the best predictors for the presence of CAD.

DISCUSSION

The main goal of this study was to assess the relation between plasma lipid, lipoprotein and apolipoprotein measurements and CAD. Because visual readings of coronary angiograms are known for only a moderate degree of accuracy, we undertook the present study using a widely accepted quantitative method of measuring coronary arterial stenoses.5 In addition, we paid special attention to Lp(a), which recent studies have shown to have a positive correlation with angiographically demonstrated CAD in both native vessels and saphenous venous bypass grafts. 8-12 The latter reports depended on a visual estimation of the extent of CAD and frequently on only qualitative measurement of Lp(a). With methods for an Lp(a) assay now commercially available, we were able to include quantitative determinations of Lp(a) in our apolipoprotein measurements. However, it is well known that a uniform standard among different laboratories is lacking. Additionally, Lp(a) is heterogenous in size and density, and it has recently been shown that Lp(a) consists of ≥6 different phenotypes. 19 Thus, immunometric methods could be highly dependent upon the antigenic sites of the antibodies that are used for the

Our results show that lipid measurements were statistically different between the groups of patients with and without CAD. However, the proximity of the means of the 2 groups is too close to be clinically useful. In particular, serum Lp(a) provides a wide spread of results but has a large standard deviation that detracts slightly from its use as a possible screening tool. However, for the individual patient with CAD, it may play an important role in the disease process. Note that discrepancies with other studies may exist because of differences in patient selection as well as methodologic deficiencies.

The results showed no correlation between levels of lipoprotein and apolipoproteins and the severity of CAD. This was to be expected because atherosclerosis is a disease of unknown cause with many predisposing factors. Common, well-recited coronary risk factors (e.g., smoking, diabetes and hypertension) did not independently predict the presence of coronary plaques. These

factors may relate importantly to thrombotic events (plaque activity) and less to the degree of narrowing. Our results with logistic regression analysis provide some estimate as to the relative strength of each variable in the prediction of the presence of hemodynamically important CAD. As was shown previously, family history and age play strong roles in the prediction of CAD. Apo B also has a predictive value in both sample populations. However, when Lp(a) was entered into the mode (group B), the serum HDL to total cholesterol ratio lost much of its predictive value.

Additionally, multivariate analysis suggested that, in group A, correct classification of patients with and without CAD would be 83 and 71%, respectively. With the addition of Lp(a) (group B), correct classification of patients with and without CAD would be 83 and 77%, respectively. Note, however, that cut points located from this study, if used in different patient subsets, may result in lower rates of correct classification. With regard to patients free of demographic risks, the percentage of accuracy of the multivariate analysis was too small to give results of any clinical usefulness.

Measurements of plasma concentrations of lipids and apolipoproteins, although useful in identifying some groups at high risk for the development of CAD, do not detect the very important qualitative changes in lipoprotein structure and functions that may be produced at or near the arterial wall. Yet such qualitative changes may enhance the atherogenic potencies of lipoproteins by altering the interactions between lipoproteins and arterial components. Researchers have recently reported on a strong correlation between serum Lp(a) and Lp(a) present in human aortas in areas of atherosclerosis. 20 Cushing et al²¹ showed an accumulation of apo (a) in diseased coronary bypass grafts undergoing replacement. Measurement of these interactions may be a more effective discriminator between CAD patients and patients with normal coronary arteries.

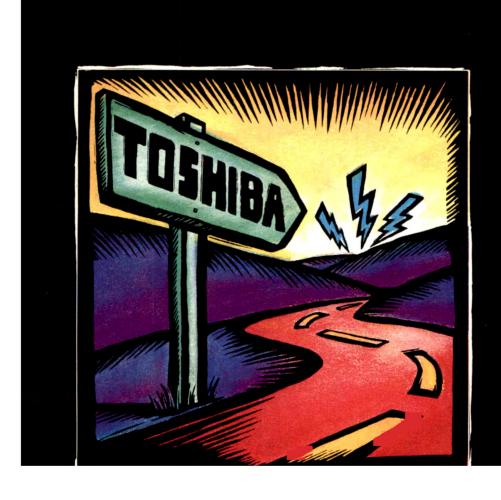
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Voltage Criteria of Left Ventricular Hypertrophy in Sudden and Nonsudden Coronary Artery Disease Mortality: The Italian Section of the **Seven Countries Study**

Mariapaola Lanti, MD, Paolo Emilio Puddu, MD, and Alessandro Menotti, MD

It is unclear whether sudden or nonsudden death can be predicted independently from other risk factors for coronary artery disease (CAD). Therefore, this investigation was undertaken to measure 12lead QRS voltage sum, a recently proposed (Am J Cardiol 1985;55:485-494) index of left ventricular (LV) hypertrophy, and its ability to predict either subsequent sudden (<2 hours) or nonsudden CAD death during 20 to 23 years of follow-up in 1,588 middle aged men (40 to 61 years old) from 2 cohorts of the Italian section of the Seven Countries Study who were free of demonstrable CAD (at entry examination in 1962). The Sokolow-Lyon and the modified Sokolow-Lyon indexes, 2 standard electrocardiographic methods to detect LV hypertrophy were also measured and compared. During follow-up, 67 patients died suddenly and 87 died a nonsudden CAD death. In the Cox proportionalhazards model, age, mean blood pressure, heart rate, body mass index, cholesterol, physical activity, smoking habit, ST-T alterations (Minnesota codes 4.1 to 4.3 together with 5.1 to 5.3) and the 3 electrocardiographic indexes, all measured at the time of enrollment into the study, were included. The 12-lead QRS voltage sum retained significant and independent relation to sudden death (t = 2.00); Sokolow-Lyon index entered the Cox solution for nonsudden CAD death but the association was inverse (t = -2.10). ST-T alterations were significantly associated only with nonsudden CAD death (t = 2.19).

Thus, in addition to several known risk factors, measurement of 12-lead QRS voltage sum in middle-aged men without clinical evidence of heart disease may help identify subjects at an increased risk of sudden death; nonsudden CAD death is predicted

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by Sokolow-Lyon index and by ST-T alterations. The usefulness of these indexes needs to be tested in different populations.

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The association of electrocardiographic left ventricular (LV) hypertrophy¹⁻⁴ with increased cardiovascular mortality or sudden death, or both, has been investigated both from epidemiologic and clinical⁵⁻⁸ points of view. High voltage with⁷⁻¹⁰ or without^{5,9,10} ST-T alterations was frequently considered. Although reports from Framingham indicate that increased QRS voltage alone does not provide independent risk of cardiovascular death, the reverse is true when the latter was combined with ST-T changes. 7,8 However, there is no published study in which sudden versus nonsudden fatalities were distinguished on the basis of voltage criteria of LV hypertrophy.

This investigation was triggered by the potential usefulness of a recently identified voltage index of LV hypertrophy⁴ and targeted at discriminating sudden versus nonsudden death due to coronary artery disease (CAD). A comparison with 2 established indexes of LV hypertrophy by electrocardiogram¹⁻³ was also performed.

METHODS

Study population: The Seven Countries Study is an ongoing longitudinal investigation of the natural history, epidemiology and etiology of adult cardiovascular diseases in men from 7 countries, including Italy where 2 cohorts were enrolled in 1960 (Crevalcore and Montegiorgio, 2 agricultural districts, respectively, in Northern and Central Italy); a third one (Italian Railroad cohort) was added in 1962.

The present analysis covered 2 of the 3 cohorts: 979 from Crevalcore and 768 from the Italian Railroad cohort, originally aged 40 to 61 years. The subjects from Crevalcore were examined in 1962 as part of an interim investigation to check the willingness of the initially enrolled men to participate in follow-up visits. Only data from 2 cohorts were analyzed here since the 1962 electrocardiograms from Montegiorgio were missed.

The methodologic details of this study are well known and have been extensively reported.5 Collection of data included the recording of a resting electrocardiogram in 12 classic leads and followed the standard

TABLE I Mean Values ± Standard Deviations and Skewness Coefficients of the Study Variables

			The second secon	
	Variable	Mean ± SD	Skewness	
	Age (yrs)	50 ± 6	-0.02	
1	Cholesterol (mg/dl)	204 ± 41	0.37	
	Smoking habit*	5±2	0.02	
	Physical activity*	2±1	-0.77	
	Body mass index (kg/m²)	26 ± 4	0.56	
ı	Mean blood pressure (mm Hg)	106 ± 13	0.75	
	Heart rate (beats/min)	74 ± 14	1.05	
	Sokolow-Lyon index (mm)	26±8	0.52	
	Modified Sokolow-Lyon index (mm)	30±8	0.52	
	12-lead QRS voltage sum (mm)	153 ± 33	0.45	

*Coded according to reference 6 as follows: Smoking habit—never smoked and ex-smokers = 3; smokers (cigarettes/day)—1 to 4 = 4, 5 to 9 = 5, 10 to 19 = 6, 20 to 29 = 7, 30 or more = 8. Physical activity—sedentary = 1, moderate = 2, and heavy = 3. ST-T alterations (Minnesota codes 4.1, 4.2 and 4.3 together with 5.1, 5.2 and 5.3) were considered among the study variables: these were present in 31 (code 1) and absent in 1,557 (code 0) subjects.

methods adopted and described by the Seven Countries Study.5 Mortality data were collected during 20 to 23 years of follow-up. Deaths were coded according to the eighth revision of the International Classification of Diseases and then converted into the Seven Countries Study internal codes.5

Study variables: Resting electrocardiograms, recorded at entry, were reviewed in each subject. In addition, age, serum cholesterol, mean blood pressure (calculated with the formula: mean blood pressure = diastolic blood pressure + 0.333 [systolic blood pressure diastolic blood pressure]), smoking habit and physical activity (both coded as follows: smoking habit-never smoked and ex-smokers; smokers: 1 to 4, 5 to 9, 10 to 19, 20 to 29, and ≥30 cigarettes/day; physical activity—sedentary, moderate and heavy⁶), and body mass index (calculated by the formula: weight in kg/height in m2) were considered. Heart rate was measured from the electrocardiogram as 60 beats/RR interval. Each RR was a mean value of ≥5 consecutive beats.

Moreover, in order to take into account ST-T abnormalities, Minnesota codes 4.1, 4.2 and 4.3 along with 5.1, 5.2 and 5.3 were included among the study variables (coded as 1 or 0, when present or absent, respectively). Extrasystoles (Minnesota code 8.1) were treated similarly as a distinct covariate.

The following electrocardiographic indexes of LV hypertrophy were calculated: (1) 12-lead QRS voltage sum⁴; (2) Sokolow-Lyon index¹; and (3) modified Sokolow-Lyon index.^{2,3} For these purposes, voltage (in millimeters; 10 mm = 1 mV) of QRS in 12 standard leads, and of S wave in leads V₁ and V₂ and of R wave in leads V₅ and V₆ were calculated by 1 observer (ML) from measurements obtained manually in 5 consecutive complexes, to prevent respiratory influences. The following definitions were used: (1) 12-lead QRS voltage sum: arithmetical sum of the 12-lead QRS voltages; (2) Sokolow-Lyon index: S wave in V₁ + the greater Rwave voltage in either leads V₅ or V₆; (3) modified Sokolow-Lyon index: the greater S-wave voltage in either leads V₁ or V₂ + the greater R-wave voltage in either leads V₅ or V₆. These indexes were treated as continuous variables.

The percentage technical error¹¹ in the measureme of 12-lead QRS voltage sum was assessed by the san observer who recalculated voltages in 90 randomly s lected electrocardiograms. Percentage technical err was calculated as: $\Sigma d2/\sqrt{(2N-1)}$ where d = diffe ence between the values obtained from the 2 measur ments and N = 90. It was found to be equal to 0.29% the mean.

For the purpose of the present study and based of Seven Countries Study death codes,⁵ 2 end points we defined: (1) sudden witnessed death (<2 hours), n 67; and (2) nonsudden CAD death (nonsudden fat myocardial infarction + heart failure + chronic failu + chronic arrhythmias attributed to CAD), n = 8 The abovementioned 2 end points comprised all CA deaths observed in this study. Another 81 deaths o curred as the consequence of stroke and peripheral at erosclerotic disease, and 345 persons died a noncardi vascular death. The 436 persons who experienced tl latter forms of death were considered as censored for the purposes of this investigation. Also, censored pe sons were the 67 sudden and the 87 nonsudden deatl in the analysis of nonsudden and sudden death predi tion, respectively.

Exclusion criteria: Of the total population, 159 were excluded from the analysis: 99 because of 1 or more missing data among those considered in this investigation tion, and 60 because of prevalence codes of heart di ease from those coded 00 to 10.5

Statistical analysis: The analysis was performed us ing BMDP programs¹² and an IBM 43/41 compute Mean values, standard deviations and skewness coeff cients were obtained for all variables considered.

Age-adjusted death rates were calculated withi equinumeric quartiles (n = 397) of 12-lead QRS vol age sum, Sokolow-Lyon, and modified Sokolow-Lyo index values for each end point. The 95% confidence limits were also computed.

The Cox proportional-hazards model was used^{12,1} to select possible risk factors for the abovementioned end points. The assumed limits for significance to ente or to remove a term were p <0.05 and p >0.05, respec tively.

The proportionality assumption, at least for the ma jor already-recognized risk factor and for the electrocal diographic indexes, has been checked defining strata for each independent variable and plotting for each stratur j, the ln (-ln S [ti;z]), where z is the mean of covariate as suggested by Kalbfleish and Prentice. 14 Except fo the first period of follow-up, when the number of event was small, the curves were seen to have approximatel constant differences over time, and then the proportion ality assumption holds.

RESULTS

Table I is a summary of mean values ± standard deviations and skewness coefficients for all variable considered. All continuous variables were normally dis tributed (that is, they were not significantly skewed).

Age-adjusted sudden and nonsudden CAD deatl rates within equinumeric quartiles of 12-lead QRS volt

TABLE II Age-Adjusted Sudden and Nonsudden CAD Death Rates (%) Within Equinumeric (n = 397) Quartiles of the Three Electrocardiographic Indexes of LV Hypertrophy and the 95% Confidence (Lower and Upper) Limits

	L	II .	III	IV
12-lead QRS voltage sum				
Sudden death	3.0 (1.3-4.7)	3.0 (1.3-4.7)	3.9 (1.9-5.7)	7.1 (4.6-9.6)*‡
Nonsudden death	8.1 (5.4–10.8)	3.8 (1.9-5.7)	4.8 (2.7–6.9)	5.3 (3.1–7.5)
Sokolow-Lyon index				0.0 (0.1 7.0)
Sudden death	2.8 (1.2-4.4)	4.5 (2.5–6.5)	3.3(1.5-5.1)	6.3 (3.9-8.7)*§
Nonsudden death	8.1 (5.4–10.8)	3.8 (1.9–5.7)	5.0 (2.8–7.1)	5.1 (2.9–7.3)
Modified Sokolow-Lyon index			0.0 (2.0 7.1)	3.1 (2.3-7.3)
Sudden death	3.5 (1.7-5.3)	3.5 (1.7-5.3)	4.8 (2.7-6.9)	5.1 (2.9-7.3)
Nonsudden death	8.6 (5.8–11.3)	3.5 (1.7–5.3)	5.1 (2.9–7.3)	4.8 (2.7–6.9)†

^{*} p <0.02; † p <0.05 (z test between proportions: quartile I vs quartile IV).
† p <0.005; § p <0.05 (trend test in proportions).
CAD = coronary artery disease; LV = left ventricular.

age sum, Sokolow-Lyon, and modified Sokolow-Lyon index values are summarized in Table II. Upper and lower 95% confidence limits are also listed. This table offers the results of a bivariate analysis which enables quick inspection of overlapping intervals. Both the proportions and the 95% confidence limits show that 12lead QRS voltage sum and Sokolow-Lyon index, but not the modified Sokolow-Lyon index, discriminate sudden death in our population (z test between quartiles I and IV gives p <0.02 for both; significant chi-squares are also observed with the trend test in proportions). Table II also shows that the highest proportions for sudden death of all 3 electrocardiographic indexes of LV hypertrophy are observed in quartile IV, whereas the highest proportions for nonsudden CAD death are seen in quartile I.

The stepwise multivariate analysis was performed taking into account all covariates previously described. However, the low prevalence of ectopic beats (n = 7)prevented one from considering these latter into the Cox model. Table III provides the Cox proportional-hazards model solutions for the 2 end points considered in the study. The solution for sudden death comprised age, heart rate, mean blood pressure and 12-lead QRS voltage sum, all of which had a positive coefficient. Age, mean blood pressure, smoking habit and ST-T alterations entered the nonsudden solution with a positive coefficient, whereas physical activity and Sokolow-Lyon index were present with a negative coefficient. In an attempt to verify the coefficient of ST-T alterations for the sudden death end point, all the covariates that were present in the final stepwise solution (Table III) and the covariate that coded ST-T alterations were forced into a Cox model. ST-T alterations showed a negative nonsignificant coefficient (-0.6738, t = -0.66).

DISCUSSION

Over 20 to 23 years of follow-up in a cohort of middle-aged men without clinical evidence of heart disease at entry examination,5 CAD-related sudden and nonsudden deaths were predicted by voltage criteria of LV hypertrophy: 12-lead QRS voltage sum appears to be an independent predictor of sudden death, whereas the Sokolow-Lyon index was inversely related to nonsudden death. This was true when these latter indexes were

treated as continuous variables, and when age, mean blood pressure, heart rate, body mass index, cholesterol, physical activity, smoking habit and ST-T alterations were taken into account. The prognostic value of age, mean blood pressure, heart rate, smoking habit and physical activity has been deeply investigated and repeatedly confirmed, and these variables represent standard risk factors in cardiovascular epidemiology. 5,15-20 These covariates will not be addressed specifically in this discussion.

Choice of electrocardiographic indexes of left ventricular hypertrophy: Autopsy, roentgenographic, angiographic or echocardiographic studies aimed at assessing the presence of LV hypertrophy concur that electrocardiography may reflect anatomic hypertrophy of the left ventricle, but sensitivity and specificity depend on the type of electrocardiographic measurement tested and on the type of comparison chosen. 1-4,21,22 Autopsy correlations with LV hypertrophy diagnosed by electrocardiogram²⁻⁴ seem to be the most reliable because the actual LV mass is taken into account. Roberts and Podolak4 compared 18 electrocardiographic criteria of LV

TABLE III Stepwise Cox Proportional-Hazards Model Solution for Either Sudden (n = 67) or Nonsudden (n = 87)CAD Death in 1,588 Persons

-1					
	Variable	Coeff.	SE Coeff.	t	Exponential
	Sudden Dea	ith			
	Age	0.0749	0.0236	3.17	1.0778
	HR	0.0185	0.0084	2.21	1.0186
	MBP	0.0191	0.0092	2.07	1.0192
	QRS	0.0073	0.0037	2.00	1.0073
	Nonsudden	Death			
	Age	0.1306	0.0218	5.99	1.1395
	MBP	0.0363	0.0083	4.38	1.0370
	Smoke	0.2202	0.0660	3.33	1.2463
	Phys. ac.	-0.4181	0.1373	-3.05	0.6583
	Sok	-0.0315	0.0150	-2.10	0.9690
	ST-T	1.0291	0.4696	2.19	2.7985

For t values more than 1.96 = p < 0.05. Coeff. - coefficient; DF = degrees of freedom; HR = heart rate; MBP = mean blood pressure; Phys. ac. = physical activity; QRS = 12-lead QRS voltage sum; Smoke = smoking habit; Sok = Sokolow-Lyon index; ST-T = ST-T alterations (see Table I).

^{19 (}sudden death) 4: global chi-square = 3 DF = 6: global chi-square = 83.91 (nonsudden death).

hypertrophy with autopsy results in 23 hearts weighing ≥1,000 g. The QRS voltage criterion that showed the highest sensitivity (94%) was the sum (>175 mm) of the voltage of the QRS complexes in all 12 standard leads. The Sokolow-Lyon index with the usual 35-mm upper limit was not a sensitive indicator of LV hypertrophy (sensitivity 71%), whereas the modified Sokolow-Lyon index had a fairly good sensitivity (88%) in that study.4 All the abovementioned indexes of electrocardiographic LV hypertrophy represent measurable (quantitatively) voltage criteria.

Left ventricular hypertrophy, high blood pressure, ST-T alterations and risk of cardiac fatalities: Rabkin,9 reviewing electrocardiographic abnormalities in apparently healthy men and the risk of dying suddenly, stressed that relative risk of sudden death varies from 1.6 to 6.94 (univariately) when classic ORS voltage criteria, with or without ST-T changes, were taken into account as evidence of LV hypertrophy. However, it has been pointed out more recently that considering electrocardiographic patterns indicative of LV hypertrophy has little effect in identifying subjects at risk for sudden unexpected death, multivariately, although it might be useful in persons with known CAD.²³ Nonsudden fatalities were generally investigated among overall CAD mortality cases. 7,8 Voltage criteria of LV hypertrophy without ST-T alterations were unable to predict these events multivariately, when blood pressure was also con-

The independent contribution of voltage criteria of LV hypertrophy or ST-T abnormalities, or both, considered as separate covariates, also in the presence of blood pressure, was not explored in previous investigations. 7-9,23 Our data suggest that voltage indexes of LV hypertrophy may predict coronary events, either sudden or nonsudden, independently from blood pressure. ST-T alterations do not contribute significantly to the prediction of sudden death, although nonsudden deaths are predicted, in conjunction with other well-known risk factors, by the Sokolow-Lyon index and by ST-T alterations. However, in previous investigations, dichotomic criteria of LV hypertrophy were adopted7,8 and this might explain, at least in part, differences from our study in which continuous variables were used for LV hypertrophy and mean blood pressure (Table III).

Although voltage criteria of LV hypertrophy were useful to predict cardiac fatalities in our study, a striking result was that 12-lead ORS voltage sum was positively related to sudden death, whereas an inverse relation existed between the Sokolow-Lyon index and nonsudden death. It is difficult to explain the reason for this latter inverse relation. We therefore compared mean values of the study variables in quartiles of the 3 LV hypertrophy indexes. In persons who die suddenly, body mass index was lower in quartile IV than in quartile I, for Sokolow-Lyon (p <0.02) and modified Sokolow-Lyon (p <0.01) indexes; mean blood pressure and cholesterol were higher for modified Sokolow-Lyon index (p <0.05 and 0.02, respectively), mean blood pressure was higher (p < 0.001) and smoke was lower (p < 0.02) for 12-lead QRS voltage sum. In persons who died a

nonsudden CAD death, body mass index was lower in quartile IV than in quartile I (p <0.05) for both Sokolow-Lyon and 12-lead ORS voltage sum. Moreover, because the negative coefficient of the Sokolow-Lyon index shown in Table III might be due to the U-shaped distribution of the risk for nonsudden death carried by such index (Table II), quadratic terms for both body mass and Sokolow-Lyon indexes were entered into a Cox model: preliminary evidence of true curvilinearity for the Sokolow-Lyon index was obtained. On the other hand, because of the very long follow-up of the study. there might have been a competition of risks^{24,25} for sudden versus nonsudden CAD death of high versus low voltages. However, when assessing the rates of sudder and nonsudden death at 5, 10, 15, 20 and more than 20 years of follow-up, 9, 34, 64, 90, 100% and 10, 24, 59. 91 and 100% were seen, respectively, thus indicating that the distribution of deaths during the follow-up is similar for both end points.

Although we were able to discriminate between sudden and nonsudden death in middle-aged men, based or voltage criteria of LV hypertrophy, it appears that no clear-cut explanation for this observation comes from the study. Thus, it remains for further studies, which might be triggered by the evidence that is presented here, first to confirm and second to try to explain our

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Videodensitometry Versus Digital Calipers for Quantitative Coronary Angiography

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Single-plane left coronary angiograms in 18 patients were prospectively analyzed using videodensitometry (XR-70 system) and handheld digital calipers to compare arterial dimensions, stenosis dimensions, intraobserver variability and interobserver variability for the methods. A total of 648 arterial segments were measured, yielding a highly significant correlation between videodensitometry and caliper-determined cross-sectional area (r = 0.96, p = 0.0001). Similarly, a highly significant linear relation was observed between videodensitometry and caliper-determined diameter (r = 0.95, p = 0.0001). When data subsets for small, medium and large arterial segments were examined, higher variability in the correlation between videodensitometry and caliper-determined area was observed in the large segments (>10 mm²). In addition, caliper-estimated areas tended to be slightly smaller than videodensitometry-estimated areas in these segments. For diameter estimations, correlations between caliper and videodensitometry data were similar for the entire range of arterial segment sizes. Intra- and interobserver variability was low for both caliper and videodensitometry determination of diameter or area. Thus, over a wide range of arterial dimensions, results obtained with caliper estimates of luminal area and diameter are comparable to those obtained with videodensitometry using the XR-70 system.

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coronary angiographic analysis that obviates the need for manual or computer-assisted edge definition. Although many practical limitations exist for application of videodensitometry to long coronary artery segments, a system has been developed that uses videodensitometry to measure arterial dimensions at discrete points along the length of a vessel.^{2,3} This system (XR-70) has been validated using phantoms and postmortem specimens and has been found to be more accurate and reproducible than caliper measurements in determination of percentage stenosis. Although these validation studies established the accuracy and reproducibility of this videodensitometric technique using phantoms, no comparative data have been reported to establish the relation of measurements made with the XR-70 system and digital calipers when quantifying routine clinical cineangiograms. The objectives of the current study were to compare arterial dimensions, stenosis dimensions, intraobserver variability and interobserver variability from cineangiogram analysis using a handheld digital caliper versus the XR-70 videodensitometric system.

rideodensitometry offers a method of quantitative

METHODS

Left coronary angiograms from 18 patients undergoing elective cardiac catheterization for evaluation of chest pain were prospectively analyzed. Cardiac catheterization was performed using the standard Judkins technique, Omnipaque 350 contrast medium, a 6-inch image intensifier and 30 frame/s filming rate. Coronary angiographic catheters were 7Fr and injections were made by hand. Left coronary angiograms recorded in the 10° to 30° right anterior oblique, 10° to 30° caudal projection were used for analysis. After the initial angiogram, serial doses of intracoronary nitroglycerin were administered (5, 50 and 150 µg). After each dose (1 minute) another angiogram was recorded, for a total of 4/patient. Cine frames judged optimal for analysis were selected from end-diastolic or neighboring frames that showed the vessel segments of interest to be optimally opacified and free from overlap of side branches. For each angiogram, segments from the left main, proximal mid- and distal left anterior descending, as well as from the proximal mid- and distal circumflex or obtuse marginal coronary arteries, were measured.

Videodensitometric analysis: Videodensitometric analysis was performed with an XR-70 coronary analyzer (Vanguard Instruments Corporation, Melville, New York) in a manner similar to that previously described.^{2,3} The XR-70 system uses a film projector

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TABLE I Statistical Data for Comparison of Videodensitometry- and Caliper-Determined Areas and Diameters

Data Subset	Covariance	R	Pf	M	В	SEE	Pb
All area data	24.608	0.955	0.0001	0.972	0.5	0.014	0.0001
0-5 mm ²	2.156	0.92	0.0001	1.167	-0.15	0.031	0.0001
5-10 mm ²	2.813	0.742	0.0001	1.174	-0.675	0.094	0.0001
>10 mm ²	8.349	0.72	0.0001	0.683	4.713	0.069	0.0001
All diameter data	0.722	0.953	0.0001	1.011	0.085	0.016	0.0001
0-1.5 mm	0.033	0.701	0.0001	0.89	0.169	0.088	0.0001
1.5-2.5 mm	0.11	0.821	0.0001	1.114	-0.084	0.06	0.0001
>2.5 mm	0.196	0.79	0.0001	0.878	0.491	0.06	0.0001

Statistics are for the linear regression model:

Caliper Determined Value = M (Videodensitometry Determined Value) + B.

Pb = p value for slope of linear regression; Pf = p value for analysis of variance F test; R = Pearson's product-moment correlation coefficient; SEE = standard error of estimate for

(model XR-35, Vanguard Instruments Corporation) and a Panasonic W.V. 1500 videocamera to acquire densitometric information. Cine frames from the 35mm film were digitized by means of a dedicated microprocessor into a 512 × 512 pixel matrix with 256 gray level resolution and analyzed after twofold magnification. Calibration was achieved by detection of the outer boundaries of the catheter. Geometric area and diameter as well as percent diameter stenosis and area stenosis were computed assuming circular cross sections as previously detailed.2,3

Caliper analysis: Caliper measurements were performed with a handheld digital caliper (MAX Series Electronic Digital Caliper, Fowler and NSK). This device consists of a rotary encoder and a rack-and-pinion vernier caliper body. Coronary segment diameter was measured directly from the screen of the Vanguard XR-35 projector. The diameter of the catheter was taken as a reference point for calibration. Particular care was taken to ensure that the measurements with the calipers and videodensitometer were taken from exactly the same vessel segments as well as from the same cine frames. Coronary artery area was later calculated from measured vessel diameter assuming circular geometry.

Statistical analysis: The relation between videodensitometric area and caliper-determined area as well as caliper diameter and videodensitometric diameter were characterized by linear regression, analysis of variance and covariance. Intra- and interobserver variability were established by a repeated analysis of 10 stenotic and 40 normal segments performed 4 weeks later by the original observer and 2 independent observers who were blinded to their original measurements. Reproducibility was measured by linear regression analysis of the blinded observations.

RESULTS

The study population included 18 men aged 40 to 76 years (mean 59). A total of 162 coronary segments were studied (144 nonstenotic and 18 stenotic segments) to comprise a total of 648 measurements. The relation between videodensitometry- and caliper-determined areas

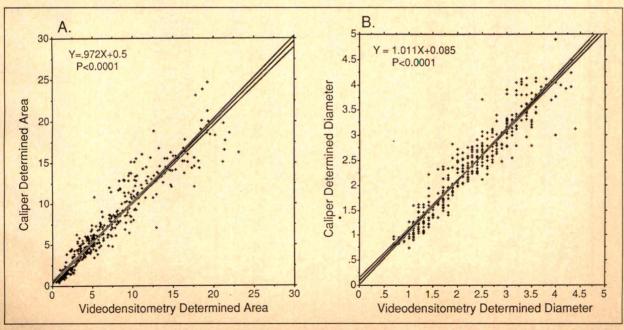


FIGURE 1. Relation between area (A) and diameter (B) determined by videodensitometry and caliper methods as described in the text; 95% confidence limits for the slope of the regression line are shown.

is shown in Figure 1. A highly significant correlation was observed between the area determinations with narrow confidence bands. Pertinent regression, analysis of variance and covariance parameters are listed in Table I.

The relation between videodensitometry- and caliper-determined diameters is also shown in Figure 1. Again, a highly significant correlation with narrow confidence bands was observed (Table I). If observations are divided by videodensitometric area into small (0 to 5 mm²), medium (5 to 10 mm²) and large (>10 mm²) arteries, the relation between videodensitometry- and caliper-determined areas becomes more variable. These findings are shown in Figure 2 and corresponding statistical data are included in Table I. Correlation between videodensitometry and caliper measurements of vessel area is closer in smaller arteries than in larger ones. In addition, the slope of the relation between videodensitometry- and caliper-determined areas decreases as arterial size increases. In the range of 0 to 10 mm² the

slope of the relation between videodensitometric and caliper areas is slightly >1, whereas in arteries >10 mm² the slope is <1 with a larger Y intercept. A similar analysis of diameter data is presented in Figure 3. Variability in the relation between videodensitometry- versus caliper-determined diameter is similar to that for area data. Unlike correlations for area data, correlations for videodensitometry and caliper diameter values show a similar value for small (0 to 1.5 mm), medium (1.5 to 2.5 mm) and large (>2.5 mm) segments.

The results of interobserver variability analysis are presented in Figures 4 and 5. Multiple observations by 3 operators of videodensitometric and caliper estimates of luminal area and diameter did not yield coefficients of correlation under $r^2 = 0.856$. There was no significant difference in correlation between the 2 methods for estimation of luminal area and diameter. Intraobserver variability data shown in Figure 6 demonstrate a high degree of reproducibility for both videodensitometric and caliper analysis of luminal area and diameter.

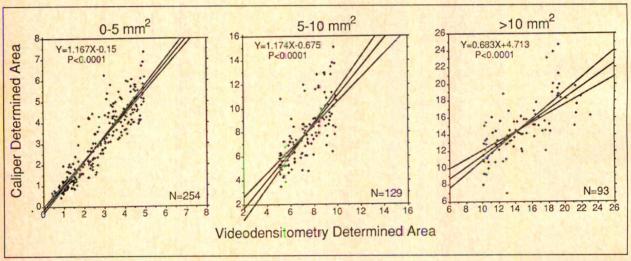


FIGURE 2. Relation between videodensitometry-determined area and caliper-determined area for small, intermediate and larger vessel segments.

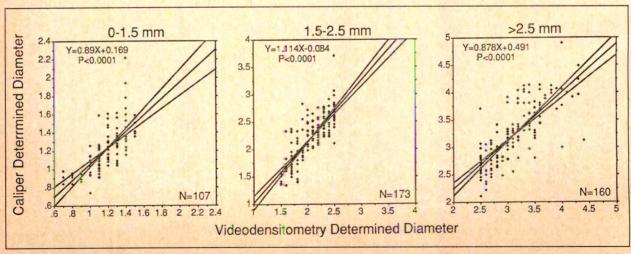


FIGURE 3. Relation between videodensitometry-determined diameter and caliper-determined diameter for small, intermediate and larger vessel segments.

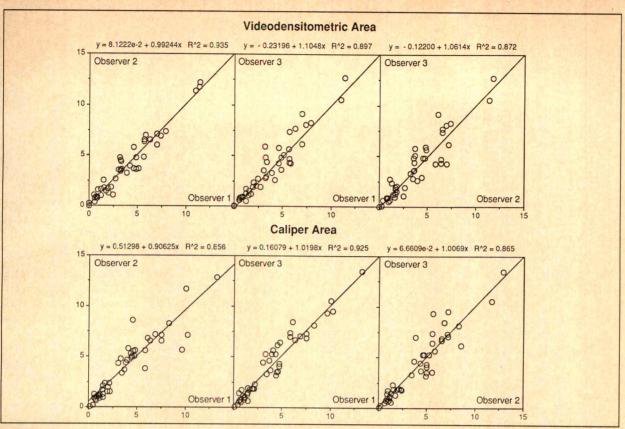


FIGURE 4. Interobserver variability data for area measurements by caliper and videodensitometric methods as described in the text.

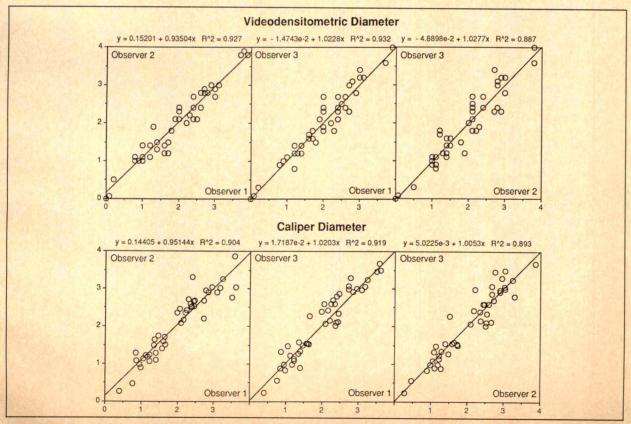


FIGURE 5. Interobserver variability data for diameter measurements by caliper and videodensitometric methods as described in the text.

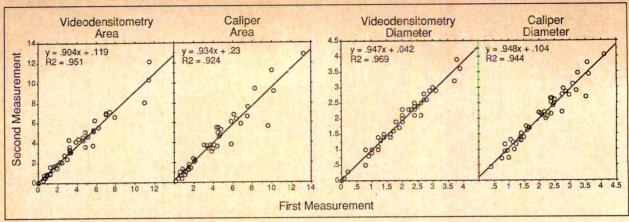


FIGURE 6. Intraobserver variability data for caliper and videodensitometric techniques as described in the text.

DISCUSSION

The major findings of the current study are: (1) there is a highly significant correlation between handheld caliper and computer-assisted videodensitometric estimates of coronary luminal area and diameter made with the XR-70 system; and (2) intra- and interobserver variability with both methods is acceptably low. Since the videodensitometric method used herein has been previously validated using phantoms,2 agreements between caliper and videodensitometric data in this study provide indirect evidence for the validity of caliper-determined dimensions in other investigations. Scoblionko et al4 reported that measurements of percent stenosis made by digital electronic calipers and the computerized quantitative method described by Brown et al5 did not differ significantly; however, both of those methods require manual edge detection. In the present study we compared a method dependent on manual edge detection (calipers) with an independent method (videodensitometry). In another preliminary report, 6 the correlation between quantitative computerized arteriography and caliper estimates of percent stenosis was also found to be good (r = 0.86, standard error of the estimate = 8.3%). However, in both of these studies, the investigators did not report on the correlation for luminal area.

The excellent correlation between caliper and videodensitometric measurements existed over a wide range of arterial calibers. When data for arteries of different calibers are considered separately, in large coronary arteries, diameter and area were slightly lower by the caliper method. In small arteries and stenoses, caliperdetermined area values tended to be slightly higher than those by videodensitometry, whereas the converse was true for diameter estimates. Other investigators⁶ have shown an overestimation of stenosis diameter by the caliper method when compared to an automated digital quantitation technique. Because the actual dimensions of the coronary arteries in the current study are unknown, further meaningful analyses regarding the accuracy of caliper and videodensitometric measurements are not possible.

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Easy-to-handle nonadhesive tab

See revised Dosage and Administration section in brief summary of Prescribing Information on the following page.

All transdermal nitroglycerin products are being marketed pending final evaluation of effectiveness by the FDA.

Transderm-Nitro® nitroglycerin_0.1 mg/hr, 0.2 mg/hr, 0.4 mg/hr, 0.6 mg/hr



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At the heart of nitrate compliance

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Easy to apply — Easy to remove

Available in four convenient strengths

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Transderm-Nitro® nitroglycerin

Transdermal Therapeutic System

Revised Dosage Information

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)

INDICATIONS AND USAGE

INDICATIONS AND USAGE
This drug product has been conditionally approved by the FDA for the prevention of angina pectoris due to coronary artery disease. Tolerance to the antianginal effects of nitrates (measured by exercise stress testing) has been shown to be a major factor imiting efficacy when transdermal nitrates are used continuously for longer than 12 hours each day. The development of tolerance can be altered (prevented or attenuated) by use of a noncontinuous (intermittent) dosing schedule with a nitrate-free interval of 10-12 hours.

Controlled clinical trial data suggest that the intermittent use of nitrates is associated with decreased exercise tolerance, in companison to placebo, during the last part of the nitrate-free interval; the clinical relevance of this observation is unknown, but the possibility of increased frequency or severity of angina during the nitrate-free interval should be considered. Further investigations of the tolerance phenomenon and best regimen are ongoing. A final evaluation of the effectiveness of the product will be announced by the FDA.

CONTRAINDICATIONS

Allergic reactions to organic nitrates are extremely rare, but they do occur. Nitroglycerin is contraindicated in patients who are allergic to it. Allergy to the adhesives used in nitroglycerin patches has also been reported, and it similarly constitutes a contraindication to the use of this product

warnings
The benefits of transdermal nitroglycerin in patients with acute myocardial infarction or congestive heart failure have not been established. If one elects to use nitroglycerin in these conditions, careful clinical or hemodynamic monitoring must be used to avoid the hazards of hypotension and tachycardia.

A cardioverter/defibrillator should not be discharged through a paddle electrode that overlies a Transderm-Nitro patch. The arcing that may be seen in this situation is harmless in itself, but it may be associated with local current concentration that can cause damage to the paddles and burns to the patient.

PRECAUTIONS

General
Severe hypotension, particularly with upright posture, may occur
with even small doses of nitroglycerin. This drug should therefore
be used with caution in patients who may be volume depleted or
who, for whatever reason, are already hypotensive. Hypotension
induced by nitroglycerin may be accompanied by paradoxical
bradycardia and increased angina pectoris.

Nitrate therapy may aggravate the angina caused by hypertrophic
cardiomyoathy

Nitrate therapy may aggravate the angine cooled your cardiomyopathy. As tolerance to other forms of nitroglycerin develops, the effect of sublingual nitroglycerin on exercise tolerance, although still observable, is somewhat blunted. In industrial workers who have had long-term exposure to unknown (presumably high) doses of organic nitrates, tolerance clearly occurs. Chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitrates from these workers, demonstrating the existence of true chysical dependence.

nitrates from these workers, demonstrating the existence of true physical dependence.

Several clinical trials in patients with angina pectoris have evaluated nitroglycerin regimens which incorporated a 10-12 hour nitrate-free interval. In some of these trials, an increase in the frequency of anginal attacks during the nitrate-free interval was observed in a small number of patients. In one trial, patients demonstrated decreased exercise bolerance at the end of the nitrate-free interval. Hemodynamic rebound has been observed only rarely; on the other hand, few studies were so designed that rebound, if it had occurred, would have been detected. The importance of these observations to the routine, clinical use of transdermal nitroglycerin is unknown.

transdermal nitroglycerin is unknown.

Information for Patients

Daily headaches sometimes accompany treatment with nitroglycerin. In patients who get these headaches, the headaches may be a marker of the activity of the drug. Patients should resist the temptation to avoid headaches by altering the schedule of their treatment with nitroglycerin, since loss of headache may be associated with simultaneous loss of antianginal efficacy.

Treatment with nitroglycerin may be associated with lightheadedness on standing, especially just after rising from a recumbent or seated position. This effect may be more frequent in patients who have also consumed alcohol.



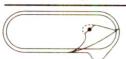
0.1 mg/hr... Formerly designated as 2.5 mg/24 hr



0.2 mg/hr... Formerly designated as 5 mg/24 hr



0.4 mg/hr... Formerly designated as 10 mg/24 hr



0.6 mg/hr... Formerly designated as 15 mg/24 hr

After normal use, there is enough residual nitroglycerin in discarded patches that they are a potential hazard to children and pets.
A patient leaflet is supplied with the systems

A patient leaner is supplied with the systems.

Drug Interactions

The vasodilating effects of nitroglycerin may be additive with those of other vasodilators. Alcohol, in particular, has been found to exhibit additive effects of this variety.

Marked symptomatic orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustments of either class of agents may be necessary.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No long-term animal studies have examined the carcinogenic or
mutagenic potential of nitroglycerin. Nitroglycerin's effect upon
reproductive capacity is similarly unknown.

Pregnancy Category C
Animal reproduction studies have not been conducted with
nitroglycerin. It is also not known whether nitroglycerin can cause
tetal harm when administered to a pregnant woman or whether it
can affect reproductive capacity. Nitroglycerin should be given to a
pregnant woman only if clearly needed.

Nursing Mothers

It is not known whether nitroglycerin is excreted in human milk

It is not known whether nitroglycerin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when nitroglycerin is administered to a nursing woman.

Pediatric Use Safety and effectiveness in children have not been established

ADVERSE REACTIONS

ADVERSE REACTIONS
Adverse reactions to nitroglycerin are generally dose-related, and almost all of these reactions are the result of nitroglycerin's activity as a vasodilator. Headache, which may be severe, is the most commonly reported side effect. Headache may be recurrent with each daily dose, especially at higher doses. Transient episodes of lightheadedness, occasionally related to blood pressure changes, may also occur. Hypotension occurs infrequently, but in some related it have be represented to a research describingtion of

may also occur. Hypotension occurs infrequently, but in some patients it may be severe enough to warrant discontinuation of therapy. Syncope, crescendo angina, and rebound hypertension have been reported but are uncommon.

Extremely rarely, ordinary doses of organic nitrates have caused methemoglobinemia in normal-seeming patients. Methemoglobinemia is no infrequent at these doses that further discussion of its diagnosis and treatment is deferred (see Overdosage).

Application site irritation gray court hat its carely express.

Application-site irritation may occur but is rarely severe. In two placebo-controlled trials of intermittent therapy with nitroglycerin patches at 0.2 to 0.8 mg/hr, the most frequent adverse reactions among 307 subjects were as follows:

Placebo	Patch
18%	63%
4%	6%
0%	4%
2%	2%
	18% 4% 0%

OVERDOSAGE

OVERDOSAGE
Hemodynamic Effects
The ill effects of nitroglycerin overdose are generally the result of nitroglycerin's capacity to induce vasodilatation, venous pooling, reduced cardiac output, and hypotension. These hemodynamic changes may have protean manifestations, including increased intracranial pressure, with any or all of persistent throbbing headache, confusion, and moderate fever; vertigo; palpitations; visual disturbances; nausea and vomiting (possibly with colic and even bloody diarrhea); syncope (especially in the upright posture); air hunger and dyspnea, later followed by reduced ventilatory effort, diaphoresis, with the skin either flushed or cold and clammy; heart block and bradycardia; paraylssis coma; seizures, and death

diaphoresis, with the skill effect interfect of cold and claiming, hear block and bradycardia; paralysis; coma; seizures; and death. Laboratory determinations of serum levels of nitroglycerin and its metabolites are not widely available, and such determinations have in any event, no established role in the management of nitroglycerin overdose.

have in any event, no established role in the management of nitroglycerin overdose.

No data are available to suggest physiological maneuvers (e.g., maneuvers to change the pH of the unne) that might accelerate elimination of nitroglycerin and its active metabolites. Similarly, it is not known which, if any, of these substances can usefully be removed from the body by hemodialysis.

No specific antagonist to the vasodilator effects of nitroglycerin is known, and no intervention has been subject to controlled study as a therapy of nitroglycerin overdose. Because the hypotension associated with hitroglycerin overdose is the result of venodilatation and arterial hypovolemia, prudent therapy in this situation should be directed toward an increase in central fluid volume. Passive elevation of the patient's legs may be sufficient, but intravenous infusion of normal saline or similar fluid may also be necessary. The use of epinephrine or other arterial vasoconstrictors in this setting is likely to do more harm than good.

In patients with renal disease or congestive heart failure, therapy resulting in central volume expansion is not without hazard. Treatment of nitroglycerin overdose in these patients may be subtle and difficult, and invasive monitoring may be required.

Methemoglobinemia
Nitrate ions liberated during metabolism of nitroglycerin can oxidize hemoglobin into methemoglobin. Even in patients totally without cytochrome b₁ reductase activity, however, and even assuming that the nitrate moleties of nitroglycerin are quantitatively applied to oxidation of hemoglobin, about 1 mg/kg of nitroglycerin should be required before any of these patients manifests clinically significant (≥ 10%) methemoglobinemia. In patients with normal reductase (2 10%) intertemognotherma. In patients with normal reductase function, significant production of methemoglobin should require even larger doses of nitroglycerin. In one study in which 36 patients received 2-4 weeks of continuous nitroglycerin therapy at 3.1 to 4.4 mg/hr, the average methemoglobin level measured was 0.2%; this was comparable to that observed in parallel patients who received placeby.

received placebo.

Notwithstanding these observations, there are case reports of

Notwithstanding these observations, there are case reports or significant methemoglobinemia in association with moderate overdoses of organic nitrates. None of the affected patients had been thought to be unusually susceptible. Methemoglobin levels are available from most clinical laboratories. The diagnosis should be suspected in patients who exhibit signs of impaired oxygen delivery despite adequate cardiac output and adequate arterial pO₂. Classically, methemoglobinemic blood is described as chocolate brown, without color change on exposure to air.

When methemoglobinemia is diagnosed, the treatment of choice is methylene blue, 1-2 mg/kg intravenously.

DOSAGE AND ADMINISTRATION

DUSAGE AND ADMINISTRATION
The suggested starting dose is between 0.2 mg/hr*, and
0.4 mg/hr*. Doses between 0.4 mg/hr* and 0.8 mg/hr* have
shown continued effectiveness for 10-12 hours daily for at least
one month (the longest period studied) of intermittent administration. Although the minimum nitrate-free interval has not been
defined, data show that a nitrate-free interval of 10-12 hours is
sufficient (see INDICATIONS AND USAGE). Thus, an appropriate
dosing schedule for nitroglycerin patches would include a daily
patch-on period of 12-14 hours and a daily patch-off period of
10-12 hours.

Although some well-controlled clinical trials with the second

Although some well-controlled clinical trials using exercise Although some wen-controlled clinical trials using exercise tolerance lesting have-shown maintenance of effectiveness when patches are worn continuously, the large majority of such controlled trials have shown the development of tolerance (i.e., complete loss of effect) within the first 24 hours after therapy was initiated. Dose adjustment, even to levels much higher than generally used, did not restore efficacy.

PATIENT INSTRUCTIONS FOR APPLICATION OF SYSTEM

HOW SUPPLIED Total

Transderm- Nitro System*	Nitro- glycerin in System	System Size	Carton Size
0.1 mg/hr	12.5 mg	• •	30 Systems NDC 57267-902-26 30 Systems NDC 57267-902-42 00 Systems NDC 57267-902-30
0.2 mg/hr	25 mg	10 cm ²	30 Systems NDC 57267-905-26 30 Systems NDC 57267-905-42 00 Systems NDC 57267-905-30
0.4 mg/hr	50 mg	20 cm ²	30 Systems NDC 57267-910-26 30 Systems NDC 57267-910-42 00 Systems NDC 57267-910-30
0.6 mg/hr	75 mg	30 cm ²	30 SystemsNDC 57267-915-26 30 SystemsNDC 57267-915-42 100 SystemsNDC 57267-915-30

^{**}Institutional Pack

Rated release in vivo. Release rates were formerly described in terms of drug delivered per 24 hours. In these terms, the supplied Transderm-Nitro systems would be rated at 2.5 mg/24 hr (0.1 mg/h), 5 mg/24 hr (0.2 mg/hr), 10 mg/24 hr (0.4 mg/hr), and 15 mg/24 hr (0.6 mg/hr)

Do not store above 86°F (30°C)

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Brady EM, Gold OG, Rosenbach HJ. Antianginal efficacy of transdermal nitroglycerin and oral nitrates: The ACTION Study. Cardiovasc. Rev. Rep. October 1988: 40-44.

Frequency of Myocardial Indium-111 Antimyosin Uptake After Uncomplicated Coronary Artery Bypass Grafting

Bob van Vlies, MD, Eric A. van Royen, MD, Cees A. Visser, MD, Nico G. Meyne, MD, Monique M. G. van Buul, MD, Ron J. G. Peters, MD, and Arend J. Dunning, MD

The reported incidence of myocardial damage after coronary artery bypass grafting (CABG) is highly related to the methods used. Since indium-111 monoclonal antimyosin antibody scintigraphy has been shown to be highly specific and sensitive for myocardial necrosis, even in small lesions, uptake of this radiotracer was evaluated after CABG. In 23 consecutive patients without previous myocardial infarction who underwent CABG for stable angina, 80 MBq indium-111 antimyosin was injected on the third postoperative day. Planar images were obtained 48 hours later and analyzed for myocardial uptake of indium-111 antimyosin. Scintigraphic results were related to creatine kinase MB levels, duration of both aortic cross-clamping and cardiopulmonary bypass, and electrocardiographic changes. In all patients surgical procedure and postoperative course was uncomplicated. Indium-111 antimyosin uptake was present in 19 of 23 patients (82%). It was diffused in 7 patients and localized in 12. No pathologic Q waves occurred postoperatively. Fourteen patients exhibited STsegment changes. No good relation was found among indium-111 antimyosin uptake and creatine kinase MB levels, duration of cross-clamping or bypass, and ST-T changes. It is concluded that some degree of myocardial damage, though silent, is common after CABG.

(Am J Cardiol 1990;66:1191-1195)

oronary artery bypass grafting (CABG) has been shown to be an effective treatment in relieving symptoms caused by myocardial ischemia. Improved surgical skills, anesthesiologic techniques and myocardial protection, all aimed at preventing myocardial injury, have enhanced outcome.² Nevertheless, myocardial damage after CABG is not infrequent.^{3,4} The amount of damage appeared to be an important determinant for postoperative mortality and morbidity. 5,6 The incidence of perioperative myocardial infarction has been reported to range from about 5 to >40%. This range is due to differences in diagnostic procedures and diverging reference values. Routinely used tests for diagnosing acute myocardial infarction, enzyme measurements and electrocardiography have-in this respect—proved to be of limited value.⁴ In a postmortem study, subendocardial contraction band necrosis, a result of reperfusion injury, was demonstrated in regions with well-functioning bypass grafts in >80% of patients.7 Recently Weisel et al8 demonstrated myocardial membrane damage after cardioplegia due to free oxygen-derived radicals.

Indium-111 antimyosin scintigraphy has proved to be highly specific for myocardial necrosis,⁹ and localized uptake of this monoclonal antibody has been demonstrated even in small and nontransmural myocardial lesions.¹⁰ Therefore, the present study was undertaken to investigate the uptake of this radiopharmaceutic as a measure of myocardial damage in patients after uncomplicated CABG.

METHODS

Patient selection and surgical procedure: The study group consisted of 23 consecutive patients, 18 men and 5 women, mean age 60.6 years. All patients underwent elective CABG for stable angina (New York Heart Association class III). None of the patients had a history of myocardial infarction, congestive heart failure or cardiac surgery. Three-vessel disease was documented in 16 patients, 2-vessel disease in 5 and 1-vessel disease in 2. Informed consent was given according to the criteria of the institutional ethics committee, which had approved the study.

During surgery all patients were subject to routine anesthesiologic and monitoring procedures. During cardiopulmonary bypass St. Thomas' cardioplegic solution was used in combination with systemic hypothermia (27° C). An average of 3.9 ± 1.5 vessels was grafted.

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From the Departments of Cardiology, Nuclear Medicine and Thoracic Surgery, Academic Medical Center, Amsterdam, the Netherlands. This study was presented at the 39th annual meeting of the American College of Cardiology, March 1990, New Orleans, Louisiana. Manuscript received April 9, 1990; revised manuscript received and accepted July 10, 1990.

No. Pts.	No. Grafts	Antimyosin Uptake	CK MB (IU/I)	ST Change	ACC (min)	CPB (min)
1	1	diffuse	12		12	33
2	1	localized	21	-	22	35
3	2	diffuse	13	+	26	57
4	2	negative	14	-	30	76
5	3	localized	33	-	30	54
6	3	localized	35	+	51	73
7	3	localized	29	+	38	75
8	3	negative	42	_	46	77
9	3	localized	36	+	54	95
10	4	negative	20	+	50	83
11	4	diffuse	87	-	52	87
12	4	localized	27	_	54	90
13	4	localized	99	+	57	102
14	4	diffuse	18	+	74	113
15	5	negative	80	-	48	83
16	5	localized	58	_	54	87
17	5	diffuse	51	+	65	91
18	5	localized	29	+	56	96
19	5	localized	20	+	66	105
20	5	localized	27	+	66	128
21	6	diffuse	25	+	87	126
22	6	localized	23	+	62	126
23	7	diffuse	145	+	93	144

Mean aortic cross-clamp time was 51 ± 19 minutes; bypass time was 88 ± 27 minutes.

Biochemical and electrocardiographic measurements: Initial blood samples for creatine kinase MB measurement were taken postoperatively at 6-hour intervals during 24 hours, or longer, when values were still increasing. The normal laboratory level for creatine kinase MB is ≤4 IU/liter. At our institution a value of 70 IU/liter is arbitrarily used as the upper normal limit in patients after cardiac surgery. Electrocardiograms were obtained the day before imaging and evaluated for the presence of Q waves with a duration of ≥0.04 second or for changes of the ST-segment or T wave compared with preoperative registrations.

Indium-111 antimyosin administration and imaging: For the antimyosin studies, a murine monoclonal antibody Fab fragment (Myoscint®, Centocor Europe) was used. Eighty MBq of indium-111 was added to a single vial containing 2 ml of antimyosin-Fab-DTPA preparation in citrate buffer. The labeling efficiency was >95%.

Indium-111 antimyosin was injected intravenously on the third day after surgery. All drain systems had been removed ≥24 hours earlier without signs of ongoing pericardial leakage.

Planar images were obtained after 48 hours in the anterior and 45° left anterior oblique position. A General Electric Maxi 400 large-field-of-view gamma camera was used, fitted with a medium energy collimator. A 20% energy window was set to the 170 and 247 keV photon peak. Analog and digital images for each view were acquired for a 10-minute period, using a 128 X 128 matrix for the latter. All studies were assessed by 2 experienced investigators unaware of clinical and biochemical data. When present, myocardial uptake was defined as localized or diffuse.

Statistical analysis: All data are expressed as mean \pm 1 standard deviation. Student t tests are used to analyze differences between groups. A p value <0.05 was considered significant.

RESULTS

Clinical characteristics: Complications during the postoperative course occurred in only 1 patient, who had sternal infection. In all other patients clinical course was uneventful.

The mean creatine kinase MB isoenzyme level was 41 ± 32 IU/liter (range 12 to 145). In 19 patients a peak value ≤70 IU/liter was present, whereas 4 patients had a peak value >70 IU/liter.

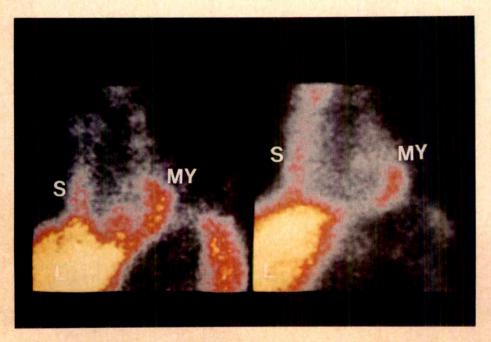


FIGURE 1. Two indium-111 antimyosin scintigrams (left anterior oblique view) obtained on the fifth postoperative day after injection on the third day. Right panel shows localized posterior uptake. Left panel shows diffuse myocardial uptake. L = liver; MY = myocardium; S = ster-

In none of the patients did pathologic Q waves appear on the electrocardiogram after surgery. In 14 patients ST-segment or T-wave changes were present (individual data are listed in Table I).

Indium-111 antimyosin scintigraphy: No side effects were noticed after injection of indium-111 antimyosin. Images could be obtained in all 23 patients. In 19 patients (82%) myocardial uptake of indium-111 antimyosin was demonstrated (Figure 1); uptake was localized in 12 patients and diffuse in 7. In 4 patients no uptake was found. All but 1 of these 4 patients had a creatine phosphokinase MB peak value of ≤70 IU/liter, the postoperative upper normal limit. Only in 3 of the 19 patients with myocardial uptake did creatine kinase MB value exceed the level of 70 IU/liter. In the other 16 patients creatine kinase MB value was above the laboratory normal limit, but ≤70 IU/liter. There was no good relation between the type of antimyosin uptake (negative, local or diffuse) and creatine kinase MB levels (Figure 2). Electrocardiographic changes involving the ST-segment or T wave occurred in all 3 groups. Again, no differences between patients with local uptake versus patients with diffuse uptake were found (Figure 3).

There proved to be no good relation between aorta cross-clamp time $(43 \pm 8, 58 \pm 28, 51 \pm 13 \text{ minutes})$ or duration of cardiopulmonary bypass $(80 \pm 3, 93 \pm 35, 89 \pm 26 \text{ minutes})$ and degree of indium-111 antimyosin

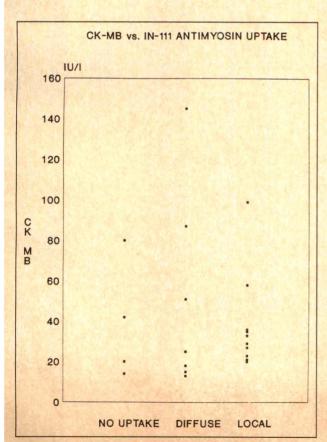


FIGURE 2. Relation between creatine kinase MB (CK MB) levels and degree of indium-111 (IN-111) antimyosin uptake. A substantial overlap is evident.

uptake (Figures 4 and 5). Mean values did not differ significantly.

Indium-111 antimyosin uptake was present in the 2 patients with 1-vessel disease and in 17 of 21 patients with multivessel disease. Localized uptake was consistently situated in grafted areas.

DISCUSSION

Since myocardial injury is a major prognostic determinant after cardiac surgery, data on its incidence and extent may be important. However, controversy exists regarding the frequency and clinical implications of postoperative myocardial infarction. The incidence highly depends on the selection of patients and the techniques used to measure myocardial damage. Furthermore, several preoperative factors may predispose to postoperative myocardial infarction, such as recent infarction, depressed left ventricular function, extent of coronary artery disease and unstable angina.11 The changing profile of patients undergoing CABG—that is, increasing emergency procedures, patients with unstable angina, CABG in the elderly, combined procedures—increases the risk.12 Finally, anesthesia-related problems, inadequate myocardial protection and a long duration of both aorta cross-clamping and cardiopulmonary bypass may also contribute to myocardial injury. 13 The assessment of the presence and magnitude of myocardial necrosis after CABG is difficult. Mechanisms of onset, clinical presentation and even ultrastructural characteristics of postoperative myocardial damage differ from the classic type of myocardial infarction. 14 This

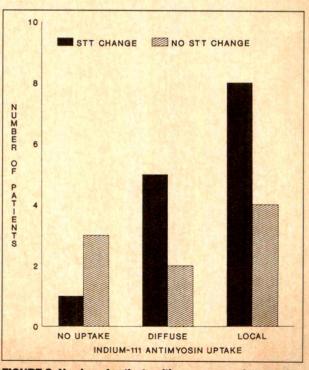


FIGURE 3. Number of patients with presence or absence of ST-segment or T wave (STT) changes. ST-T changes occurred in all groups. No difference was present when patients with diffuse or local uptake of indium-111 antimyosin were compared.

difference may complicate the interpretation of routine diagnostic tests. Furthermore, methodologic differences in various studies, although using the same test, complicate the comparison of results. Routine tests, such as enzyme measurements and electrocardiography, give rise to diverging and unsatisfying results. Postoperative myocardial infarction is diagnosed in about 5% of patients when the appearance of new Q waves is used, whereas the number goes up to 40% when ST-segment changes are taken into account.15 The presence of new O waves is strongly related to postoperative myocardial infarction, but their absence will underestimate the incidence of small, especially subendocardial lesions. Creatine kinase MB isoenzymes, the gold standard for the diagnosis of myocardial infarction, are elevated in almost all patients after CABG, 16 but their clinical relevance in the absence of other signs of postoperative myocardial infarction remains doubtful.

Infarct imaging with technetium-99m pyrophosphate has been reported to be positive in more than 20% of patients after CABG.¹⁷ This technique, however, is known to have a lower sensitivity in the setting of subendocardial necrosis, 18 which is the most frequent site of perioperative myocardial damage. Also, studies on left ventricular wall motion are conflicting, and improvement¹⁹ as well as deterioration of function^{20,21} have been demonstrated.

Because the imaging technique used herein is highly specific for myocardial damage, the following question has to be answered in the light of the present findings: What is a normal test result in this particular population? Some myocardial necrosis may be almost obligatory after CABG, but the favorable outcome in the majority of patients emphasizes the limitation of its importance. Despite all precautions before and during operation, coronary bypass surgery seems to be an insult to the myocardium. Acute changes in hemodynamics, temperature changes and direct contact with surgical instruments will damage myocardial cells. Additionally, reperfusion of previously ischemic myocardium may be harmful and may lead to necrosis. 22,23 Bulkley et al7 reported the postmortem results in patients who died within 30 days after CABG. They found evidence in 48 of 58 patients (83%) for subendocardial contractionband necrosis, which is one of the pathologic features of reperfusion injury, 22,24 localized in areas with widely patent bypass grafts. They concluded that reperfusion injury was common after CABG. Weisel et al8 demonstrated the generation of free oxygen radicals after cardioplegic arrest leading to membrane damage in myocardial biopsy specimens obtained during surgery.

In the present study all patients had an elevated creatine kinase MB level when compared to the normal reference value in a healthy population. Only 4 patients

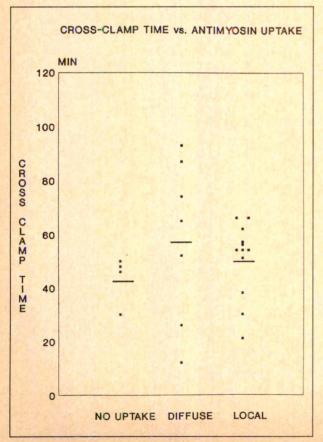


FIGURE 4. Relation between aorta cross-clamp time (in minutes) and indium-111 antimyosin uptake. Mean values, indicated by black lines, do not differ significantly.

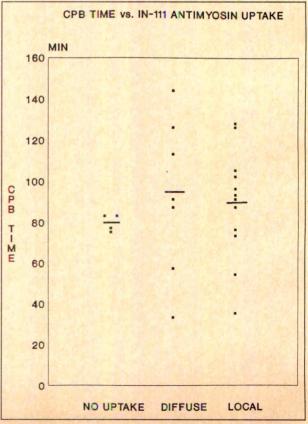


FIGURE 5. Relation between cardiopulmonary bypass (CPB) time (in minutes) and indium-111 (IN-111) antimyosin uptake. Mean values, indicated by black lines, do not differ significant-

(17%) had a value >70 IU/liter, used as the normal upper limit after CABG, a percentage in keeping with the data of McGregor et al.25 Indium-111 antimyosin scintigraphy showed uptake in 82% of our patients and gave evidence for myocardial necrosis, which did not affect clinical course. The incidence of perioperative necrosis in our patients, assessed with indium-111 antimyosin, is in keeping with the postmortem data of Bulkley et al.7 However, they studied a highly selected population. Our data, in contrast, were obtained in patients with an uneventful postoperative course in whom the previously mentioned factors, which may predispose for postoperative myocardial infarction, were also absent. This indicates that some degree of myocardial damage may be a common phenomenon even after uncomplicated surgery. Furthermore, indium-111 antimyosin uptake was not related to the duration of aorta cross-clamping or cardiopulmonary bypass.

A gold standard for the diagnosis of postoperative myocardial infarction does not exist. Myocardial injury, however, seems to be frequent, and related to the surgical procedure. When it will become relevant for clinical course, or to what extent it may be accepted as normal in this particular situation, should be the subject of further study. Comparison of patients who have an uneventful course with patients who have overt perioperative damage is needed. Quantification of indium-111 antimyosin uptake will be necessary to use it as a discriminating technique. Moreover, the relation with changes in left ventricular function has to be studied, since only clinical course was considered; however, there were no signs of hemodynamic deterioration.

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Usefulness of High-Frequency Analysis of Signal-Averaged Surface Electrocardiograms in **Acute Myocardial Infarction Before and After Coronary Thrombolysis for Assessing Coronary Reperfusion**

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The incidence of late potentials on the signal-averaged electrocardiogram before and after coronary thrombolysis was studied in 54 patients with an acute myocardial infarction of ≤5 hours' duration and with an angiographically documented total occlusion of the infarct-related coronary artery on admission. A significant (p = 0.038) 50% relative reduction in the incidence of late potentials was observed in the group of 35 patients who underwent reperfusion: from 16 of 35 (46%) before to 8 of 35 (23%) at 120 minutes after the start of thrombolytic treatment. No significant reduction was seen in the 19 patients in whom thrombolysis was unsuccessful: from 8 of 19 (42%) before to 7 of 19 (37%) afterward. Despite successful recanalization. late potentials persisted or newly developed after thrombolytic therapy in 8 of 54 patients (15%). It is concluded that successful thrombolysis reduces the incidence of late potentials on the signal-averaged electrocardiogram but that the sensitivity and specificity of this finding are not high enough to allow reliable monitoring of coronary reperfusion at the bedside.

(Am J Cardiol 1990;66:1196-1198)

Tentricular tachyarrhythmias have been associated with the presence of slow and inhomogeneous conduction within areas of damaged or ischemic myocardial tissue. The presence of these conduction abnormalities can be detected on a signal-averaged surface electrocardiogram as low-amplitude potentials in the terminal portion of the QRS complex. These bursts of low-amplitude signals, prolonging the QRS complex, are called late potentials. Several investigators have correlated the presence of late potentials with the occurrence of ventricular arrhythmias and sudden death early and late after an acute myocardial infarction.1-6

Recently, a lower incidence of late potentials has been reported in patients with acute myocardial infarction after successful thrombolysis when compared with conventionally treated patients.7,8 In another recent study,9 however, no significant effect of thrombolytic therapy on any abnormal signal-averaged variable was found at 13 days after acute myocardial infarction. In

these previous studies coronary recanalization was not documented by repeated angiography. The present study was designed to evaluate the effect of angiographically proven coronary reperfusion on the incidence of late potentials and to test the possible value of this technique as a noninvasive tool for bedside monitoring of early coronary reperfusion and reocclusion.

METHODS

Patients: Patients ≤70 years of age with acute myocardial infarction of ≤5 hours' duration and with STelevations of ≥2 mm in at least 2 adjacent electrocardiographic leads could enter the trial provided that no contraindications to thrombolytic therapy were present. Only patients in normal sinus rhythm without bundle branch block and with a total occlusion of the infarctrelated coronary artery at angiography performed on admission (see below) were selected for the study.

Signal-averaged electrocardiogram: A signal-averaged electrocardiogram (1200 EXP, Arrhythmia Research Technology, Inc.) was obtained as described previously. 10 Briefly, standard orthogonal bipolar leads (X, Y and Z) were used and signals from 200 to 300 beats were amplified, digitized, averaged and then filtered

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(high band-pass filter of 40 Hz). The signals from the filtered leads were combined into a "vector magnitude" electrocardiogram. The root-mean square voltage of the terminal 40 ms of the filtered QRS complex, the duration of the filtered ORS complex and the duration of the low-amplitude (<40 µV) signals in the terminal portion of the QRS were automatically computed. Late potentials were considered present if either of the 2 following criteria were met: a low voltage signal (<20 µV) in the last 40 ms of the QRS complex or a filtered QRS duration exceeding 120 ms. 1,10 Recordings were obtained before thrombolytic therapy, after the 90-minute angiogram and on the third hospital day.

Coronary angiography: All patients who fulfilled the entry criteria were submitted to an acute catheterization using the brachial approach. The state of perfusion was graded from 0 (complete occlusion) to 3 (full patency) according to the criteria of the Thrombolysis in Myocardial Infarction Study Group. 11 Angiograms of the infarct-related vessel were made before and after the intracoronary injection of 200 µg nitroglycerin. If the infarct-related coronary artery remained occluded after nitroglycerin, 50 to 70 mg of recombinant tissuetype plasminogen activator (rt-PA) was given intravenously over 2 to 5 minutes. Repeated angiograms of the infarct vessel were recorded at 60 and 90 minutes in all patients and also at 12 to 48 hours in case of complete reperfusion (grade 3) at the 90-minute angiogram. At 60 to 90 minutes, an additional dose of 20 mg of rt-PA could be given if the infarct-related artery was grade 2 or less, whereby a maintenance infusion of 1,000 IU hour of heparin was begun.

Statistical analysis: Continuous variables are given as mean ± standard deviation. The frequency of observations in the 2 groups, before and after thrombolysis, was tested for statistical significance with a McNemar test.

RESULTS

Serial signal-averaged electrocardiograms could be recorded in 54 patients (46 men, 8 women) aged 33 to 68 years (mean 53). On admission, electrocardiographic signs of inferior wall acute myocardial infarction were present in 29 patients. In 25 patients the anterior wall was involved.

At angiography performed on admission, 25 patients had a total occlusion of the left anterior descending coronary artery, 27 had total occlusion of the right coronary artery and 2 had occlusion of the circumflex coronary artery. In all patients the infarct-related vessel remained occluded after intracoronary injection of 200 µg of nitroglycerin. Thrombolytic therapy was begun between 87 to 300 minutes after the onset of symptoms (mean delay 233 ± 50 minutes). Reperfusion (grades 2 and 3) was documented at 90 minutes in 35 patients (65%): 18 with a left anterior descending and 17 with a right coronary artery lesion. In 19 patients (35%), no reperfusion (grades 0 and 1) was achieved: 7 with a left anterior descending, 10 with a right and 2 with a circumflex coronary artery lesion. In 4 of 35 patients with a patent (grade 3) infarct vessel at 90 minutes, reocclusion was documented at control angiography performed 12 to 48 hours after start of thrombolytic therapy.

Relation between coronary reperfusion and incidence of late potentials: The first signal-averaged electrocardiogram was recorded between 85 and 240 minutes after the onset of symptoms (mean delay 180 minutes). Late potentials were present in 24 patients (44%). On a second signal-averaged electrocardiogram, recorded 120 ± 15 minutes after the start of thrombolytic treatment, only 15 patients (28%) had late potentials. The incidence of late potentials before and after successful or failed thrombolysis in the total group is shown in Figure 1. In the 35 patients who had reperfusion, 16 (46%) had late potentials before recanalization compared with only 8 (23%) afterward (a significant 50% relative reduction: p = 0.038). In 19 patients in whom thrombolysis failed, the incidence of late potentials before and after treatment was 42% (8 patients) and 37% (7 patients), respectively. In 10 of 16 patients with late potentials before treatment in whom reperfusion was successful, the electrocardiogram normalized at 120 minutes (a 62% relative reduction). This was the case inonly 3 of the 8 patients (37%) with late potentials at entry and persistent coronary occlusion at 90 minutes. Of the 39 patients without late potentials at 120 minutes, 27 (69%) showed reperfusion (grades 2 and 3), a frequency not very different from the 53% found in the group with late potentials (8 of 15). Therefore, the specificity and sensitivity of a negative signal-averaged electrocardiogram recorded at 120 ± 15 minutes after thrombolytic therapy with regard to coronary patency are low: 69 and 47%, respectively.

Furthermore, on the third signal-averaged electrocardiogram, recorded 76 ± 5 hours after thrombolytic therapy, late potentials reappeared in 7 of the 39 patients (18%) with a negative result on electrocardiogram at 120 minutes. Five of these had a patent infarct-related vessel at 90 minutes, of whom 3 showed reocclusion on the late angiogram. One patient had reocclusion after 90 minutes without reappearance of late potentials. In 4 of 15 patients (27%) with late potentials at 120

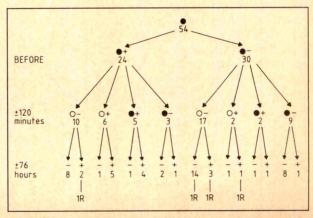


FIGURE 1. Coronary patency and frequency of late potentials before and after (\pm 120 minutes, \pm 76 hours) thrombolytic therapy. Open circles, reperfusion; closed circles, no reperfusion; + = presence of late potentials; - = absence of late potentials; R = angiographically documented reocclusion.

TABLE I Cardiovascular Complications and Death During Hospital Stay

		The state of the s
	No Late Potentials (n = 22)	Late Potentials On ≥1 Occasion (n = 32)
Death	0	2
Ventricular tachycardia and fibrillation	0	2
Reinfarction	1	3
Angioplasty, bypass surgery, or both	9	19
Shock	0	2

minutes, the signal-averaged electrocardiogram normalized at 76 hours. In 2 of these, persistent patency was documented. In the 2 other patients the vessel was occluded at 90 minutes but a late angiogram was not recorded. Thus, spontaneous, late recanalization might have occurred in the latter 2 patients.

Clinical course during hospital stay: Major clinical events and outcome are listed in Table I. Death or lifethreatening arrhythmias occurred in 4 patients. No cerebral bleedings were found.

DISCUSSION

It has been shown that thrombolytic therapy for acute myocardial infarction is associated with a significant reduction in the incidence of late potentials on the signal-averaged electrocardiogram recorded within 48 hours of admission. Furthermore, the same investigators have demonstrated a reduced incidence of late potentials in patients with a patent infarct-related coronary artery, whether patency was obtained by intervention (angioplasty or thrombolytic therapy) or spontaneously, suggesting a causal relation between coronary patency and electrical stability.12

In the present study, a signal-averaged electrocardiogram was obtained before and immediately after angiographically documented reperfusion. Only patients with a total infarct-related coronary artery occlusion on admission were selected for the study. A reduced early incidence of late potentials was observed in patients in whom thrombolysis was successful. Thus, this study confirms the findings of Gang et al7 and further supports the concept that coronary reperfusion improves electrical stability of the heart. A reduced incidence of serious ventricular arrhythmias may be one of the mechanisms responsible for improved survival after early thrombolytic therapy and may partly explain the discrepancies that are observed between the effects of thrombolytic therapy on left ventricular function and survival. 13-15

Because no signal-averaged electrocardiograms in this study were recorded at the time of hospital discharge our results cannot be compared with those of Turitto9 and Eldar8 and their associates. Significant

time-dependent changes in the signal-averaged electrocardiogram after acute myocardial infarction have been reported previously.2,16

In contrast with the findings of Gang et al, 7 a substantial number of reperfused patients in our study had late potentials after treatment and a high proportion of nonreperfused patients did not show late potentials at 2 hours after the start of thrombolytic therapy. Furthermore, angiographically documented reocclusion was associated with reappearance of late potentials in only 2 of 3 patients. Thus, the specificity and sensitivity of a negative signal-averaged electrocardiogram in this study for detecting coronary patency after thrombolytic therapy was only moderate. Therefore, this method will, most likely, be of limited value for bedside monitoring of coronary reperfusion and reocclusion.

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Time Course and Prognostic Significance of Serial Signal-Averaged Electrocardiograms After a First Acute Myocardial Infarction

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The prognostic significance of serial signal-averaged electrocardiograms recorded during the first 3 days (period 1), in the second week (period 2) after a first acute myocardial infarction (AMI) and 6 months later (period 3) was prospectively assessed in 190 patients. No patients were treated with thrombolytic therapy. Patients with conduction disturbances were excluded. Mean age of the 190 patients was 57 years (range 34 to 74) and mean left ventricular ejection fraction was 40 + 6% (range 12 to 70). Eighty-four patients had an anterior wall AMI and the remaining 106 patients an inferior wall AMI. After a mean follow-up of 24 months, 16 patients developed sustained symptomatic monomorphic ventricular tachycardia, 7 patients were resuscitated from an episode of ventricular fibrillation, and 10 patients died suddenly. Multivariate regression analysis using continuous variables showed that the strongest predictor of sustained ventricular tachycardia and ventricular fibrillation was the left ventricular ejection fraction (p <0.0001) followed by the duration of QRS complex on the signal-averaged electrocardiogram recorded during the first 3 days of AMI (p <0.0005). Sudden death was only predicted by left ventricular ejection fraction (p < 0.02).

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n patients surviving acute myocardial infarction (AMI), recognition of those at high risk of develop-Ling life-threatening arrhythmias and sudden death is of obvious importance. Size of infarction as reflected in left ventricular ejection fraction and also complex ventricular arrhythmias have been identified as important factors in this risk stratification. Recently, increasing attention has been given to the signal-averaged electrocardiogram as another screening method, alone or in combination with other parameters.2 Most of these studies have been retrospective. Recordings have been obtained at varying time intervals after AMI. Our study using serially recorded signal-averaged electrocardiograms in 190 patients was performed to (1) obtain prospective data on the value of this technique, and (2) get an insight into the most appropriate time of recording the signal-averaged electrocardiogram after AMI.

METHODS

Patients: All patients admitted to our coronary care unit in 1983 with the diagnosis of AMI were considered candidates to prospectively enter the study. Patients were excluded if (1) the diagnosis of AMI could not be confirmed even after the first recording had been obtained; (2) conduction disturbances were present at the time of recruitment; (3) technical or practical problems impeded the necessary recordings; (4) the patient was taking antiarrhythmic drugs at the time of admission with AMI; or (5) the patient had a previous AMI, had undergone bypass surgery, or had other associated cardiac or noncardiac conditions (e.g., electrolyte disturbances) that could influence the results of the signalaveraged electrocardiogram. Of 320 patients with a first AMI, 190 had no exclusion criteria and could prospectively be included in the study. No patient was treated with thrombolytic therapy. A signal-averaged electrocardiogram using Simson's method3 was recorded during 1 of the first 3 days (period 1) after onset of symptoms. The study was repeated in the second week (period 2) and, if the patient was alive, after 6 months in the outpatient clinic (period 3). Full electrical isolation during the recording was guaranteed by a specially prepared room next to the coronary care unit where no other electrical devices were present. The duration of the QRS complex and the voltage of the terminal 40 ms of the QRS complex were calculated according to the methods defined by Simson.³ Although filters for 25 and 50 Hz were used, only data using 25-Hz filters are presented because results were identical.

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TABLE I Presence of Late Potentials and Arrhythmic Events in Relation to Left Ventricular Ejection Fraction

Perio	ods Afte	rAMI	LVEF>	×40%	LVEF <40%	ó	
1	2	3	LP	AE	LP	AE	p Value
+	_	_	6	1	2	1	NS
+	+	-	6	0	4	0	NS
+	-	+	0	1	2	0	NS
	-	+	0	0	4	1	NS
+	+	+	13	5	4	7	0.02
	+	-	0	0	3	0	NS
1 × 1	+	+	0	1	0	0	NS
_	-	10 m	117	7	29	9	NS

AMI = acute myocardial infarction; AE = arrhythmic event; LP = late potentials: LVEF = left ventricular ejection; NS = not significant; period 1 = first 3 days after AMI; period 2 = week 2 after AMI; period 3 = 6 months after AMI; - (V40 >25 V) = no LP; + (V40 <25 V) = presence of LP.

In our study the voltage of the terminal 40 ms of the QRS complex (V40) was analyzed as a continuous variable and dichotomized as well. When the amplitude of signals in the last 40 ms of the filtered QRS were dichotomized, late potentials were considered present if low-amplitude voltage was $\langle 25 \mu V \rangle$. Late potentials were also categorized as normal ($\langle 25 \mu V \rangle$) or abnormal ($\langle 25 \mu V \rangle$).

In all patients information was available on age, gender, location of AMI, maximal enzyme increase, cause of death, and incidence of spontaneously occurring sustained ventricular tachycardia during follow-up. Left ventricular ejection fraction was measured before discharge using 2-dimensional echocardiography, left ventricular contrast angiography or nuclear techniques. In patients in whom left ventricular ejection fraction had been measured with several of these techniques the average value was used for the calculation. As previously reported in our institution, correlation between echocardiographic and angiographic left ventricular ejection fraction and between nuclear and angiographic left ventricular ejection fraction is 0.96 and 0.94, respectively.

Statistical analysis was performed using univariate and multivariate analysis with the Cox proportional-hazards model using continuous variables with a univariate predictor value <0.10. One-way analysis of variance and simultaneous confidence intervals were used to compare the continuous variables between groups. All values are expressed as a mean ± standard deviation. The mean follow-up at time of analysis was 25 months (range 1 to 33).

RESULTS

Of the 190 patients, 37 (19%) had late potentials (V40 $<25 \mu V$) during 1 of the first 3 days (period 1) after myocardial infarction. The incidence decreased to 15% (30 of 190 patients) during the second period (2 weeks after AMI) and was 12% (23 patients) in the 178 survivors after 6 months (Table I). There were 12 deaths: 10 patients died suddenly and 2 patients died because of pump failure.

Of 142 patients with a left ventricular ejection fraction >40%, 25 patients (18%) had late potentials during

>1 of the 3 postinfarction periods in contrast to 19 of 48 patients (39%) with left ventricular ejection fraction <40% (p = 0.003).

When comparing the patients without arrhythmic events to patients with arrhythmic events (sudden death, ventricular fibrillation, ventricular tachycardia), we noted some differences among the 4 groups. The peaks of creatine kinase and oxaloacetic transferase were higher in patients with ventricular tachycardia (p <0.0001). Left ventricular ejection fraction was lower in patients having ventricular fibrillation and in those who died suddenly (p <0.0001). Mean duration of QRS in period 1 was 108 ms (range 88 to 120) in patients developing sustained ventricular tachycardia during follow-up, 120 ms (range 66 to 120) in patients with ventricular fibrillation, and 106 ms in those who died suddenly. In patients without arrhythmic events mean duration of QRS was 90 ms (p <0.0001) (Table II).

Mean voltage of the terminal 40 ms of the V40 on the first day after myocardial infarction was lower in patients with ventricular tachycardia (p <0.0001). In contrast, patients having ventricular fibrillation had a lower voltage during the second and third periods after myocardial infarction (p <0.0001).

After a mean follow-up of 25 months, there were 33 arrhythmic events, and 16 patients (8.8%) presented with symptomatic sustained monomorphic ventricular tachycardia. In 4 patients this arrhythmia was observed around the twenty-fifth day after AMI, in 4 patients approximately 1 month after AMI and in the remaining 8 patients after >13 months (range 13 to 32). Seven patients (3.8%) were resuscitated from ventricular fibrillation. Four patients had ventricular fibrillation <1 month after AMI and 3 at 1 month after AMI. Ten patients (5.5%) died suddenly. Two patients died with documented ventricular tachycardia/ventricular fibrillation after 1 month of AMI. The remaining 8 patients died suddenly and without electrocardiographic documentation before the third signal-averaged electrocardiogram was recorded (range 1 to 5.5 months). Two patients died because of pump failure approximately 15 months after AMI. Arrhythmic events occurred more often in patients with left ventricular ejection fraction <40% (15 in 48 vs 18 in 142) (p <0.01). The combination of persistent late potentials during the 3 postinfarction periods and the occurrence of arrhythmic events was also seen more often in patients with low left ventricular ejection fraction (5 in 142 vs 7 in 42) (p <0.01) (Table I).

With use of continuous variables (Cox proportional hazards), the strongest predictor of sustained ventricular tachycardia and ventricular fibrillation was found to be left ventricular ejection fraction (p <0.0001) followed by duration of the QRS complex in the signal-averaged electrogram recorded during the first 3 days of infarction (p <0.0005).

Sudden death was only predicted by left ventricular ejection fraction (p <0.02). When sudden death, ventricular fibrillation and ventricular tachycardia were taken together and the same continuous variables applied, left ventricular ejection fraction remained the

TABLE II Clinical Characteristics of Patients with Ventricular Tachycardia, Ventricular Fibrillation and Sudden Death

	No Events	VT	VF	SD
No. of pts.	157	16	7	10
Age (years)	57±3	62±2	55 ± 1	57±3
Site of MI				
Anterior	60	13	6	5
Interior	97	3	1	5
Peak CK (U/liter)	2,331 ± 30	2,879 ± 181*	$2,563 \pm 92$	$2,553 \pm 90$
Peak OT (U/liter)	260 ± 20	325 ± 15*	292 ± 13	272 ± 20
LVEF(%)	47 ± 3	39 ± 2	30 ± 4*	30 ± 5*
Mean duration QRS	90±3	108±2	120±1*	106±2
Period 1 (ms)				
Mean duration QRS	99±3	112±2*	112±1*	106 ± 2
Period 2 (ms)				
Mean duration QRS	95±3	96±2	96±1	96±2
Period 3 (ms)				
Mean V40	65±3	45 ± 3*	48±2	52±3
Period 1 (mV)				
Mean V40	52±2	43±3	34 ± 2*	62±2
Period 2 (mV)				
Mean V40	53±2	46±3	36 ± 2*	66±2
Period 3 (mV)				

* p value <0.0001.

CK = creatine kinase; LVEF = left ventricular ejection fraction; MI = myocardial infarction; OT = oxaloacetic transferase; period 1 = first 3 days after AMI; period 2 = week 2 after AMI; period 3 = 6 months after AMI; SD = sudden death; VF = ventricular fibrillation; VT = ventricular tachycardia; V40 = amplitude last 40 ms of QRS.

strongest predictor for arrhythmic events (p <0.0001), with the duration of the QRS complex from the signalaveraged electrogram recorded during the first 3 days of myocardial infarction as the second most powerful predictor.

DISCUSSION

In recent years several investigators have recorded late potentials after an AMI. 2,3,5-10 Our results suggest that left ventricular ejection fraction was the most important predictor of sudden death and the occurrence of sustained ventricular arrhythmias during follow-up. The duration of the ORS complex on the signal-averaged electrocardiogram during the first period (3 days) after AMI was an independent predictor (p <0.0005). Serial signal-averaged electrocardiograms at the second period (2 weeks) and third period (6 months after AMI) did not add additional information.

Gomes et al⁵ found good specificity (80%) and sensitivity (88%) in the duration of QRS complex in the "acute" phase of AMI, but the signal-averaged electrocardiograms were not recorded during the late phase of AMI. The same group⁶ found that left ventricular ejection fraction had an independent value from the late potentials to predict arrhythmic events. They also described that the predictive value of the signal-averaged electrocardiogram in patients with anterior wall AMI was better than left ventricular ejection fraction. Pollak et al⁷ reported that the predictive value of late potentials was independent of left ventricular ejection fraction in patients with and without ventricular tachycardia.

El-Sherif et al⁸ described that an abnormal signalaveraged electrocardiogram and a low ejection fraction had independent value for predicting late arrhythmic events after the acute phase of myocardial infarction. In their study, an abnormal signal-averaged electrocardiogram was considered a low-amplitude signal (<25 mV)

in the last 40 ms of the QRS, a total filtered QRS duration >120, or both. In our patients left ventricular ejection fraction was the strongest predictor of prognosis. Late potentials were not an independent variable in terms of prognosis.

Few studies have paid attention to the value of serial and prospectively recorded signal-averaged electrocardiograms. 8-10 Serial signal-averaged electrocardiograms showed that the most important prognostic information was recorded during the first period (3 days) after AMI. This observation is of interest both pathophysiologically and in terms of the practical application of the technique.

From the pathophysiologic point of view, one can only speculate on the serial changes observed in the signal-averaged electrocardiogram. The incidence of late potentials (as defined here) decreased from the first to the second period after AMI, with a further decrease in the survivors 6 months later. Progressive cell death may have caused the changes from the first to second period and 6 months later, but also slowing in conduction during the phase of acute ischemia. Because sudden death after AMI can be the result of other causes than a sustained ventricular arrhythmia, it cannot be expected that either the signal-averaged electrocardiogram or left ventricular ejection fraction will reach a sensitivity or specificity of 100%.

With regard to the practical application of the technique, serially recorded signal-averaged electrocardiograms demonstrate that the best prognostic value can be obtained when recordings are obtained early after AMI.9 Interestingly, our findings suggest that this is true for the duration of the QRS complex, but not for the presence of a late potential. A widened QRS on the signal-averaged electrocardiogram during the first 3 days after AMI probably indicates a large area at Our patients were admitted to the hospital at a time when thrombolytic therapy was not given. It is well known now that thrombolytic therapy after AMI leads to a reduced incidence of abnormal signal-averaged electrocardiograms. 11,12 It appears unlikely, however, that the presence of an abnormal signal-averaged electrocardiogram after thrombolytic therapy will be significantly different when compared with an abnormal signal-averaged electrocardiogram without thrombolytic therapy.

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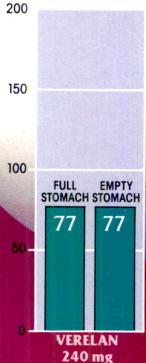
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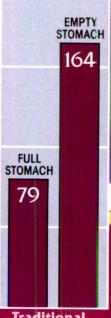
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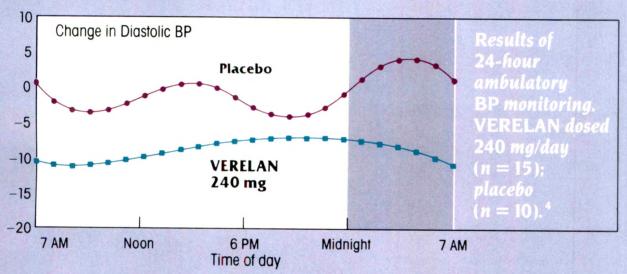
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References:
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and/or diuretics before VERELAN is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported.

Several cases of hepatocellular injury have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg. WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular librillation after receiving IV verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (second- and third-degree, 0.8%). Development of marked first-degree block or progression to second- or third-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, second-degree AV block, sinus arrest, pulmonary edema and/or severe hypotensions were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

with verapamil.

PRECAUTIONS: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil moved ecrease neuromuscular fransmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adienteground blockers and verapamil may result in additive negative effects on heart rate, active entricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol clearance may occur with combined use. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the

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The following reactions: reported in 1.0% or less of patients, occurred under conditions (open trial).

enzymes (see WARNINGS).

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Prognostic Value of Predischarge Low-Level Exercise Thallium Testing After Thrombolytic Treatment of Acute Myocardial Infarction

Peter L. Tilkemeier, MD, Timothy E. Guiney, MD, Paul J. LaRaia, MD, and Charles A. Boucher, MD

Low-level exercise thallium testing is useful in identifying the high-risk patient after acute myocardial infarction (AMI). To determine whether this use also applies to patients after thrombolytic treatment of AMI, 64 patients who underwent early thrombolytic therapy for AMI and 107 patients without acute intervention were evaluated. The ability of both the electrocardiogram and thallium tests to predict future events was compared in both groups. After a mean follow-up of 374 days, there were 25 and 32% of cardiac events in the 2 groups, respectively, with versus without acute intervention. These included death, another AMI, coronary artery bypass grafting or angioplasty with 75% of the events occurring in the 3 months after the first infarction. The only significant predictors of outcome were left ventricular cavity dilatation in the intervention group and ST-segment depression and increased lung uptake in the nonintervention group. The sensitivity of exercise thallium was 55% in the intervention group and 81% in the nonintervention group (p <0.05).

Therefore, in patients having thrombolytic therapy for AMI, nearly half the events after discharge are not predicted by predischarge low-level exercise thallium testing. The relatively weak correlation of outcome with unmasking ischemia in the laboratory before discharge may be due to an unstable coronary lesion or rapid progression of disease after the test. Tests considered useful for prognostication after AMI may not necessarily have a similar value if there has been an acute intervention, such as thrombolytic therapy.

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n stable patients after uncomplicated acute myocardial infarction (AMI), unmasking ischemia in the laboratory using low-level exercise testing before discharge has been shown to be a safe and useful procedure to identify the post-AMI patient at risk for recurrent events. 1 Thallium-201 myocardial perfusion imaging in these patients appears to be more sensitive than the electrocardiographic response to exercise in predicting subsequent cardiac events.2-5 However, the advent of acute intervention, using thrombolytic therapy, has changed the characteristics of the postinfarction population and the natural history of these patients. Therefore, the low-level predischarge exercise thallium study may not have the same prognostic usefulness in patients with versus without acute intervention. Few studies have compared the acute intervention population with the nonintervention population in terms of prognostic indicators. We evaluated 64 consecutive patients who had thrombolytic therapy at the time of AMI to assess the prognostic value of the low-level exercise thallium test before discharge in comparison with 107 consecutive patients studied during the same time period who did not undergo acute intervention at the time of AMI.

METHODS

Patient population: All 227 patients who underwent low-level exercise testing with thallium-201 imaging at the Massachusetts General Hospital within 21 days of an AMI from January 1, 1986, to February 28, 1988, were considered for inclusion in the study population. Exclusion criteria included angioplasty or coronary artery bypass graft surgery before the index AMI in 12 or lack of any follow-up data after discharge after AMI in 24. Three patients who had angioplasty as their only acute therapy were excluded. All 14 patients with prior AMI were not excluded.

Of the remaining 188, 14 had either an angioplasty or coronary artery bypass grafting during the same hospitalization as a direct outcome of an abnormal lowlevel exercise thallium test. These 14 patients were excluded from further analysis because of the potential for selection bias in considering these patients as adverse outcomes. These 14 included 3 in the acute intervention group and 11 in the nonintervention group. In addition, 3 patients died due to non-cardiac causes during followup and were therefore excluded from analysis. The remaining 171 patients who were discharged formed the

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TABLE I Clinical Data				
	No Intervention (n = 107)	Acute Intervention (n = 64)	p Value	
Age (yr)	61 ± 9	53 ± 11	0.02	
Sex (M/F)	77/30	61/6	0.02/0.02	
Prior AMI	8	6	NS	
AMI Location				
Non-Q	40	10	< 0.001	
Inferior	42	31	NS	
Anterior	23	22	NS	
Other	2	1	NS	
Follow-up interval (days)	385 ± 317	367 ± 262	NS	

Follow-up interval 385 ± 31/ 36/ ± 262 NS (days)	Angina during ETT 16 (15) 5 (9) NS (%)
AMI = acute myocardial infarction; Non-Q = non-Q-wave myocardial infarction; NS = not significant.	BP = blood pressure; ETT = exercise tolerance test; % MPHR = % maxima predicted heart rate; NS = not significant.
tudy population consisting of 107 patients who had no	protocol, 7 at the supervising physician's direction. Dur

TABLE II Exercise Data

Exercise duration (minutes) Peak heart rate

ETT interval (days)

ST depression (%) Hypotensive

BP response (%)

% MPHR

acute intervention at the time of AMI and 64 who had thrombolytic therapy (54) or thrombolytic therapy with acute angioplasty (10).

Presence of an AMI was documented by the appropriate clinical history with enzymatic (elevated creatine kinase MB fractions). The decision to use thrombolytic agents or interventional procedures, either angioplasty or coronary bypass graft surgery, was at the discretion of the individual attending physician.

Patient demographics, including age, gender, location of AMI by electrocardiographic criteria and whether it was a Q-wave or non-Q-wave infarction, were noted. These are detailed in Table I. Prior AMI (historically or by electrocardiogram), the interval from the index infarction to exercise testing and the use of interventional techniques at the time of AMI were compiled. The exercise data are detailed in Table II and consisted of the duration of exercise, the resting heart rate and blood pressure, the peak heart rate and blood pressure, the percentage of the age-predicted maximum heart rate achieved and the presence of angina during or after exercise. The presence of electrocardiographic changes during exercise that reached diagnostic criteria for ischemia (≥1 mm of ST-segment depression in leads that were normal at baseline) was also compiled.

Follow-up events: Follow-up data on the 171 patients were obtained for a minimum of 6 months or to a clinical end point. There were 2 categories of end points. One was a true adverse outcome of death or reinfarction. The other was the occurrence of any cardiac event, which included death, reinfarction, angioplasty or coronary artery bypass grafting. This identified patients who had severe disease with the potential for an adverse outcome who had been discharged after myocardial infarction without an intervention. The mean time to an event was 119 days in the nonintervention group and 105 days in the acute intervention group, with 30% of all events in both groups occurring within 4 weeks of discharge and 75% within 3 months. The mean follow-up interval was 380 days for the nonintervention group and 367 days for the intervention group. This difference was not statistically significant.

Exercise test protocol: Patients were exercised using a modified Bruce protocol⁶ or, in a minority, the Bruce ing exercise, 12-lead electrocardiograms were monitored each minute and evaluated for ST-segment abnormalities. Electrocardiograms were also taken at peak exercise, immediate recovery and at 3-minute intervals in the recovery phase. Three leads were monitored continuously throughout recovery until the electrocardiogram returned to baseline. Exercise was terminated at the discretion of the physician performing the test. Significant electrocardiographic changes (≥2 mm ST-segment depression), decrease in systolic blood pressure, or patient symptoms of angina were considered end points. A positive electrocardiographic response was ≥1 mm ST-segment depression.

Intervention

67+22

(n = 107)

 113 ± 20

 72 ± 11

 10 ± 4

37 (35)

14(13)

Intervention

7.6 + 2.6

p Value

NS

NS

NS NS

< 0.01

< 0.01

(n = 64)

119±15

 71 ± 10

 11 ± 3

10(15)

1(2)

Thallium imaging protocol: One minute before termination of exercise, 2.0 to 3.0 mCi of thallium-201 were injected intravenously and images in the anterior, left anterior oblique and 70° left anterior oblique views were obtained 3 minutes after exercise and 3 to 4 hours later.8 The images were analyzed for the presence of thallium perfusion defects and whether they were reversible or persistent. Those with redistribution were localized to either the site of the infarction or remote from it. For example, a patient who evolved an inferior O-wave infarction by electrocardiographic criteria and subsequently had an initial inferior thallium defect without redistribution would have been classified into the persistent group, whereas a patient with the same electrocardiographic evaluation and a redistributing anterior defect would have remote redistribution. The images were also analyzed for reversible or fixed exerciseinduced dilation of the ventricle. In those patients whose exercise level was adequate to clear the splanchnic bed of activity, increased lung uptake was also noted. A positive test was defined as any redistributing defect. Patients who had evidence of increased lung uptake without redistributing defects all had peak exercise heart rates of <70% of their predicted maximum and therefore lung uptake may be spuriously increased. Interpretation was by multiple experienced readers and agreement was reached by consensus.8

Statistical methods: Data were analyzed using a Student t test for determining the differences between the means of independent observations. These data were reported as a mean ±1 standard deviation. A chi-square

	No Intervention (n = 107) (%)	Acute Intervention (n = 64) (%)
Perfusion defects		
Reversible	70 (65)	26 (42)
Remote	2(2)	9(0)
Persistent	33 (31)	36 (55)
None	2(2)	2(3)
Increased lung uptake	32 (30)	14(29)
Dilated left ventricle		
Reversible	14(13)	10 (16)
Fixed	13(12)	11 (16)

TABLE IV Event Incidence					
	No Intervention (n = 107) (%)	Acute Intervention (n = 64) (%)			
Myocardial infarction	3(3)	4(6)			
Death	4(4)	1(1)			
Coronary artery bypass grafting	21 (20)	6(9)			
Angioplasty	3(3)	5 (8)			
Total	31 (32)	16 (25)			

test was used to determine the differences between proportions. A p value <0.05 was considered significant.

The sensitivity of the electrocardiogram was the number of positive electrocardiographic responses to exercise in patients with an event divided by the number of all patients who had a positive electrocardiographic response. The same is true for the thallium testing. Specificity was defined as the number of people with a negative electrocardiogram or thallium scan without an event divided by the total number of patients with either a negative electrocardiogram or thallium scan. Positive predictive value was defined as the number of patients with an event with either a positive electrocardiogram or thallium scan divided by the total number of patients with either a positive electrocardiogram or thallium scan divided by the total number of patients with either a positive electrocardiogram or thallium scan.

RESULTS

Comparison of the two groups: The exercise data for the 2 groups are presented in Table II. The 2 groups were similar in all variables except the nonintervention group had more frequent ST-segment depression and a decrease in systolic blood pressure. The results of the thallium-201 imaging are presented in Table III and are similar in both groups. The event data are tabulated in Table IV. There were no differences between the 2 groups when the incidences of myocardial infarction, cardiac death, coronary artery bypass grafting or angioplasty in the follow-up period were compared. The total number of events in both groups were similar.

Correlates of death or myocardial infarction: The individual patient data in the 12 patients with death or AMI showed that only 2 had ST-segment depression. In contrast, all but 1 patient had evidence of thallium defects, with 7 reversible and 4 persistent. Four patients had evidence of both increased lung uptake and reversible left ventricular dilatation after exercise; 3 of these

Noninterventi (n = 107) (%)		Acute Intervention (n = 64) (%)	p Value	
Sensitivity				
ECG (ST dep)	48	11	< 0.002	
Thallium (RD)	77	55	NS	
Either positive	81	55	0.03	
Both positive	45	11	< 0.01	
Specificity				
ECG (ST dep)	72	83	NS	
Thallium (RD)	37	63	< 0.01	
Either positive	76	94	< 0.005	
Both positive	33	53	0.01	
Positive predictives value				
ECG (ST deg)	42	20	NS	
Thallium (RD)	33	36	NS	
Either positive	49	30	0.04	
Both positive	44	40	NS	

had evidence of reversible thallium defects. Of the clinical, exercise and scan criteria outlined in Tables II and III, none correlated with death or AMI in either of the 2 patient populations. There was a lesser contribution of the electrocardiogram compared to thallium imaging in determining sensitivity or positive predictive value in both groups of patients.

Correlates of a cardiac event: Using all of the clinical, exercise and scan criteria in Tables II and III, in the nonintervention group, the only significant correlates of any cardiac event were ST-segment depression or increased lung uptake. There was an increased percentage of redistributing defects in the patients with events during follow-up, but this was not significant. In the acute intervention group the presence of left ventricular dilatation was the only predictor of an event in the follow-up period.

The sensitivity, specificity and positive predictive value of the electrocardiographic and thallium findings in the 2 groups are compared in Table V, and in Figures 1 and 2. The electrocardiogram had a low sensitivity with a high specificity. Thallium imaging added significantly to the sensitivity. The positive predictive value was similar for each. The sensitivity of the electrocardiogram alone or combined with the thallium results was lower in the acute intervention group compared to the nonintervention group. The specificity of the thallium results alone, either electrocardiogram or thallium results, or both, was similarly decreased in the nonintervention group compared to the acute intervention group. There were no differences between the positive predictive values of either the electrocardiogram or thallium results alone or in combination in the nonintervention and acute intervention groups.

DISCUSSION

Prognosis after AMI is determined by the severity of underlying coronary artery disease and this is assessed by demonstrating severe ventricular arrhythmia, left ventricular dysfunction or ischemia. Of these, unmasking ischemia is considered the single most important and easily treated. Predischarge low-level exercise testing with thallium-201 imaging has been one of the most common methods of demonstrating ischemia and prognostication in patients after AMI. This has been extended to patients after thrombolysis by data from the Thrombolysis in Myocardial Infarction-IIB Trial suggesting that decisions for intervention in patients after reperfusion therapy at the time of their infarction be based on the exercise thallium scan.9 The data in our study suggest that the low-level predischarge thallium exercise test provided weaker prognostic information after hospital discharge in the reperfused patient than in patients who had no acute intervention. Only 55% of all events were detected compared to 81% in the nonintervention group. Even if the 14 patients who had a predischarge angioplasty or coronary artery bypass grafting due to an abnormal exercise thallium study were included as adverse events the sensitivity would only increase to 58 and 91%, respectively. The thallium scan detected 4 of 5 (80%) of intervened patients having the most serious events, death or myocardial infarction, none of whom had ST-segment depression.

There are several possible reasons for these observations. One is that thrombolytic therapy may create an unstable situation (i.e., a partially opened vessel may reocclude). Melin et al¹⁰ addressed the issue of postthrombolytic ischemia and found a significantly greater amount of ischemia in the reperfused patient with a patent infarct-related vessel. This would support the concept of an unstable population regarding the potential for repeat cardiac events.10 The lack of detection of ischemia at the time of predischarge testing is probably due to vessel patency at the time of testing; however, ischemic events develop as the lumen narrows.

Another reason is that submaximal exercise may be an inadequate stress in this setting. Gibson et al¹¹ showed that low-level exercise (peak heart rate of 120 beats/min) with thallium imaging in the postinfarct patient accurately predicted cardiac events after uncomplicated myocardial infarction. 11 In our patients, the peak heart rate was in fact lower but not significantly different in patients with and without events. The role of dipyridamole thallium imaging has been shown to be equally safe and an acceptable alternative to predischarge low-level exercise in this patient population.12 This may avert the problem of submaximal exercise but this requires further study.

The sensitivity and specificity data obtained in this study showed a greater sensitivity for detection of cardiac events during follow-up by thallium imaging compared to the electrocardiographic exercise response in

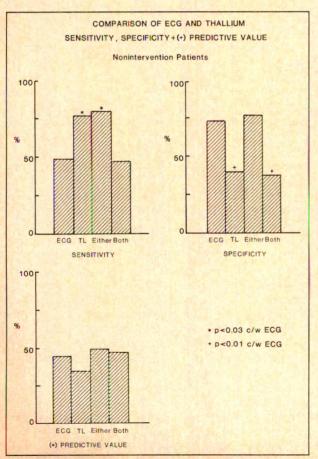


FIGURE 1. Comparison of the sensitivity, specificity and (+) predictive value of electrocardiogram (ECG) and thallium (TL) in nonintervention patients. Either is for either ECG or thallium, both is both ECG and thallium. c/w = ECG.

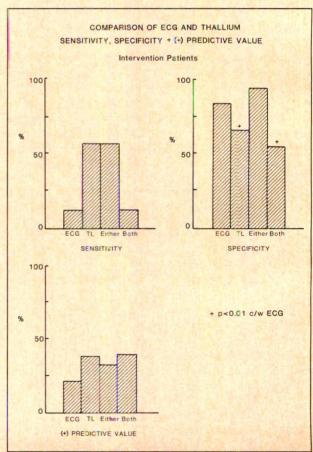


FIGURE 2. Comparison of the sensitivity, specificity and (+) predictive value of electrocardiogram (ECG) and thallium (TL) in intervention patients. Either is for either ECG or thallium, both is both ECG and thallium. c/w = ECG.

both groups. This is in agreement with Baily et al. 13 This was, however, accompanied by a lower specificity. There is clearly an increase in the sensitivity of the thallium images in the nonintervention patients with a concomitant decrease in specificity. This decrease in specificity was also present in the intervention group. When only the few natural events (e.g., death or recurrent infarction), were compared, the electrocardiogram was insensitive, with an increase in sensitivity with the addition of thallium imaging, both in the acute intervention group (0 to 80%) and in the nonintervention group (28 to 56%). This is in agreement with the findings of Turner et al3 of the complementary roll of thallium-201 imaging. However, specificity was poor and there were just as many abnormal scans in the group without death or myocardial infarction. This is in agreement with the findings of Murray et al4 and LeGrand et al5 of the limited contribution of thallium imaging to the exercise test results.

Study limitations: There were 5 limitations of our study. First, the exercise was submaximal and therefore may not reflect the maximal ischemic potential. Second, the images were obtained using the planar method and therefore the results of this study may not necessarily hold true for images acquired using tomography. Third, computer quantitation was not performed. Although quantitation has been suggested to improve image interpretation, multiple observers as used in this study have also been shown to improve image interpretation. Fourth, cardiac catheterization was not routinely performed in our patients and no conclusions regarding its relative utility or correlations could be made. Fifth, the possibility of delayed redistribution, as would be detected by 24-hour delayed imaging or imaging after reinjection at rest, was not assessed in this protocol. Thus, the percentage of patients with residual ischemia may have been underestimated. In addition, patient management decisions were not blinded to the results of the exercise thallium study.

Therefore, serious natural events (death or myocardial infarction) are relatively uncommon after uncomplicated AMI, but they are not accurately predicted by low-level testing with planar thallium imaging regardless of whether there was acute intervention at the time of infarction. This is because the specificity was poor even though the sensitivity was acceptable. In noninter-

vened patients the test did correlate with future events. mainly angioplasty and coronary bypass grafting.

In the acute intervention group, low-level exercise thallium did not predict any event, including angioplasty or bypass grafting, during follow-up, which probably resulted from progression of disease or restenosis after discharge. Further studies to evaluate different methods of follow-up will be needed to optimize prognostication. Frequent follow-up in the first year after reperfusion therapy for AMI may be helpful because late cardiac events occur in many patients with normal predischarge submaximal thallium exercise tests.

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Prognosis of Acute Myocardial Infarction Complicated by Primary Ventricular Fibrillation

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In 5,839 consecutive patients with acute myocardial infarction (AMI), hospitalized between July 1981 and July 1983 in 14 coronary care units in Israel, the incidence of primary ventricular fibrillation (VF) was 2.1%. Patients with primary VF resembled counterparts without VF in terms of age, gender, frequency of previous AMI and past cigarette smoking habits. The hospital course of patients with primary VF revealed increased incidence of primary atrial fibrillation and atrioventricular block. **Increased serum levels of glutamic oxaloacetic** transaminase and lactic dehydrogenase were noted among the patients with primary VF. In-hospital mortality rate was 18.8% in 122 patients with primary VF compared with 8.5% in 3,707 patients forming the reference group (p <0.01). Adjustment by age using logistic function yielded an estimate of 2.86 for relative mortality odds associated with primary VF, and further adjustment by gender, history of AMI, systemic hypertension, and by enzymatically estimated infarct size slightly reduced the estimated odds, at 2.52 (95% confidence interval, 1.42 to 4.46). Prognosis after discharge from the hospital was independent of primary VF. In conclusion, primary VF exerts an independent, significant effect on in-hospital mortality.

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Tentricular fibrillation (VF) remains a frequent and major, potentially lethal, complication of acute myocardial infarction (AMI). Although there is general consensus that secondary VF is associated with markedly elevated in-hospital mortality and may represent poor prognosis for survivors of AMI, opinions vary as to the prognostic value of primary VF. 1-3 We therefore undertook a study to determine the association of primary VF with in-hospital mortality after AMI.

METHODS

From 1981 to 1983 we conducted a secondary prevention study—the Secondary Prevention Reinfarction Israeli Nifedipine Trial (SPRINT)—in 2,276 survivors of AMI using nifedipine or placebo in 14 hospitals in Israel.⁴ During the study period, a logbook of all patients with AMI was maintained (SPRINT Registry). The diagnosis of AMI was confirmed by clinical electrocardiographic and enzymatic findings. Demographic and medical data were collected on special forms. Follow-up through mid-1988 was completed for all hospital survivors of the Register.

For the purpose of this study, primary VF was defined as VF complicating a first or recurrent AMI occurring within 48 hours of admission in patients in Killip class I. According to this definition, no clinical or xray signs of congestive heart failure on admission to coronary care units were recorded and neither congestive heart failure, pulmonary edema, cardiogenic shock nor persistent hypotension (systolic blood pressure <90 mm Hg/48 hours) preceded the occurrence of VF. Patients in an identical hemodynamic state (Killip class I) during their first 48 hours of hospitalization in the coronary care unit, without VF, were defined as the reference group. All patients with primary VF were connected to a monitoring system at bedside and to the central electrocardiographic monitor of the coronary care unit when the arrhythmia occurred. Immediate electrical cardioversion was provided and standard cardiopulmonary resuscitation maneuvers were begun without delay by the staff of the coronary care unit.

The SPRINT Registry of AMI, including 5,839 patients, provides a good opportunity to evaluate the incidence, the in-hospital outcome and the long-term influence of primary VF on the prognosis of survivors of acute AMI. One hundred twenty-two of these patients fulfilled the criteria of primary VF and 3,730 patients formed the reference group.

Statistical analysis: Age-adjusted prevalence of attributes correlating with primary VF has been calculated. Multivariate logistic analysis of hospital and mor-

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TABLE I Incidence of Primary Ventricular Fibrillation According to Gender, Age and Past History

	Case/Total	(%)	p Value
Men	99/4,315	(2.3)	
Women	23/1,524	(1.5)	NS
Age group (year)			< 0.05
≤50	19/671	(2.8)	
51–69	75/3,398	(2.2)	
≥70	28/1,770	(1.6)	
AMI location			NS
Anterior	52/2,565	(2.0)	
Inferior	57/2,264	(2.5)	
Non-Q-AMI	6/451	(1.3)	
Previous MI			NS
+	23/1,432	(1.6)	
0	96/4,297	(2.2)	
AP			<0.05
+	48/2,867	(1.7)	
0	69/2,790	(2.5)	
Hypertension			<0.05
+	42/2,790	(1.8)	
0	75/3,381	(2.2)	
Smoked cigarettes		To Take Vision	NS
+	62/2,758	(2.2)	
0	44/2,249	(2.0)	

AMI = acute myocardial infarction; AP = angina pectoris; NS = not significant; + =

TABLE II Characteristics of Patients with Primary Ventricular Fibrillation and of the Reference Group

	Primary VF (n = 122)		Reference (n = 3,707)			
	No.	(%)	No.	(%)	p Value	
Men	99	(81)	2,828	(76)	NS	
Age group (year)					NS	
≤50	19	(16)	542	(15)		
51-69	75	(62)	2,278	(61)		
≥70	28	(23)	887	(24)		
AMI location					NS	
Anterior	52	(43)	1,434	(39)		
Inferior	57	(47)	1,621	(44)		
Non-Q-AMI	6	(5)	322	(9)		
Previous AMI	23	(19)	700	(19)		
AP	48	(39)	1,728	(47)	NS	
Hypertension	42	(34)	1,464	(40)	NS	
Smoked cigarettes	62	(51)	1.897	(51)		
Mean age (years)	60	(31)	61	(32)	NS	

AMI = acute myocardial infarction; AP = angina pectoris; NS = not significant; VF = ventricular fibrillation.

tality after discharge yielded estimates5 of the covariateadjusted predictive power of primary VF in early (inhospital) mortality. The SAS software was utilized, specifically the FREQ6 and CATMOD7 procedures.

RESULTS

The incidence of primary VF in the SPRINT Register population was 2.1% (122 of 5,839). The latter rate did not vary markedly according to gender (men 2.3%; women 1.5%), first (2.2%) versus recurrent AMI (1.6%), age, location of myocardial infarction and anamnestic features (Table I).

The characteristics of patients with primary VF are compared with those of the reference group in Table II. Patients with primary VF had the same mean age, simi-

TABLE III Hospital Course With and Without Primary Ventricular Fibrillation

			Reference (n = 3,707)			
	No.	(%)	No.	(%)	p Value	
Congestive heart failure*	14	(12)	448	(12)	NS	
Paroxysmal AF	18	(15)	308	(8)	< 0.01	
AV block: 2nd- or 3rd-degree	22	(18)	316	(9)	< 0.001	
High enzyme level						
(>4 times upper normal levels)						
Creatine phosphokinase	71	(59)	1,969	(54)	NS	
Glutamic oxaloacetic transaminase	73	(60)	1,369	(37)	<0.05	
Lactic dehydrogenase	18	(15)	304	(8)	< 0.05	

Not observed on admission to coronary of AV = atrioventricular; other abbreviations as in Tables I and II.

TARL	EIV	In-Hospit	al Mortality

	Primary VF		Reference		
	Case/Total	(%)	Case/Total	(%)	p Value
Men	17/99	(17)	184/2,828	(7)	<0.01
Women	6/23	(26)	131/879	(15)	NS
Age (years)					
≤50	1/19	(5)	7/542	(1)	NS
51-69	9/75	(12)	158/2,278	(7)	NS
≥70	15/28	(54)	150/887	(17)	< 0.001
First AMI	12/96	(13)	240/2,972	(8)	NS
Recurrent MI	8/23	(35)	66/700	(9)	< 0.001
AP	12/48	(25)	167/1,728	(10)	< 0.001
Hypertension	7/42	(17)	128/1,464	(9)	NS
Smoked cigarettes	11/67	(16)	76/1,897	(4)	< 0.001
AMI location					
Anterior	16/52	(31)	150/1,434	(11)	< 0.01
Inferior	4/57	(7)	127/1,621	(8)	NS
Non-Q-AMI	1/6	(17)	14/322	(4)	NS

lar percent of previous AMIs but a lower incidence of angina pectoris compared with those of the reference group. The hospital course of patients with primary VF was more complicated than that in the reference group (Table III). Paroxysmal atrial fibrillation and advanced atrial ventricular block occurred about twice as often in patients whose primary VF complicated the infarction as in the reference group. High serum enzyme levels of glutamic oxaloacetic transaminase and lactic dehydrogenase were frequently found in patients with primary

The most striking finding of this study was the major effect of primary VF complicating AMI on the inhospital outcome (Table IV). Patients with primary VF had a twofold mortality rate (18.8%) compared with those in the reference group (8.5%). These statistics of higher relative risk of hospital fatalities in patients with primary VF persisted in different subsets of patients according to gender, age, and clinical history. In a logistic regression, the estimated odds ratio for hospital mortality equaled 2.86 when adjusted only for age, and 2.52 (95% confidence limits, 1.42 and 4.46) when adjusted for the combined effects of age, gender, location and

history of AMI, cerebrovascular accident and hypertension and the percent of patients with serum lactic dehydrogenase levels exceeding 4 times the upper normal limit. An appreciation of the usefulness of the analysis, is obtained by the proportion of in-hospital deaths (54.8%) occurring in those with the highest 20% probability of mortality calculated by the logistic risk function.

The excess of in-hospital mortality among patients with primary VF was due to electromechanical dissociation, cardiac rupture and standstill or intractable arrhythmia, but not due to pump failure. Thirteen patients died instantaneously from intractable arrhythmias, most occurring during recurrent chest pain with new electrocardiographic changes of ischemia, conduction disturbances, or both. Late hospital death after successful resuscitation occurred in 10 patients, 5 of whom had recurrent intractable arrhythmias.

The Kaplan-Meyer survival curve, comparing mortality in patients with primary VF with that in reference patients is shown in Figure 1. Mortality rate over the first year after discharge was 3.0% for survivors of primary VF (3 of 99 patients) and 6.5% in the reference group (difference not significant). Mortality rate through 1988 (4.5- to 6.5-year follow-up) was 16.2 and 21.2% in the primary VF and reference groups, respectively.

DISCUSSION

The SPRINT Registry of patients with AMI, based on data of a large AMI patient group collected from 14 of 21 coronary care units existing in Israel, established a reliable estimation of the incidence of primary VF. Most important, it has allowed the comparison of case fatality between patients with primary VF and counterparts receiving comparable medical care. Our results indicating a primary VF incidence of 2.1% in the coronary care unit are in accord with a number of previous studies. 9-14 We found that primary VF, complicating AMI, strongly predicted in-hospital mortality. Patients

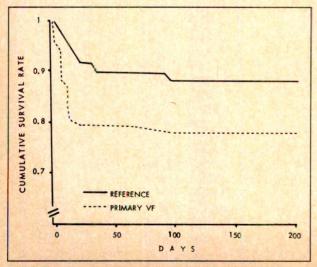


FIGURE 1. Cumulative survival rate in patients with acute myocardial infarction complicated with primary ventricular fibrillation (VF) and in the reference group patients.

with Killip class I on admission to the coronary care unit had an in-hospital mortality rate of 18.8% if they presented with primary VF and only 8.5% if they did not. This highly significant statistical difference persisted for subsets of patients according to age, gender, disease history and the location of the AMI on previous infarctions sustained by the patient, and was borne out by multivariate analysis, yielding a covariate-adjusted odds ratio of 2.52. The 95% confidence interval provides a large range for the mortality risk during the acute phase of AMI associated with primary VF, between 1.5 and 4.5; however, it probably doubles the risk.

Two recent pertinent studies reached conflicting conclusions. In the Multicenter Investigation of the Limitation of Infarct Size study,³ 40 of 815 patients who presented with primary ventricular tachycardia/VF had an in-hospital mortality rate (8%) comparable to patients without primary VF (7%). In the much larger thrombolytic study—The Italian Group for the Study of Streptokinase in Myocardial Infarction (GISSI)²—the large group of 326 patients with primary VF who had a first AMI showed twofold in-hospital mortality, as observed in comparison with the reference group (10.8 and 5.9%, respectively).

The high rate of in-hospital mortality among patients with AMI complicated by primary VF in GISSI and other clinical studies^{2,15,16} was attributed to the correlation between the size of AMI, defined enzymatically or morphologically, and the incidence of VF. In our study, patients with primary VF, although in Killip class I, exhibited a higher rate of serious cardiac complications and a higher incidence of elevated serum enzyme levels, supporting the view that AMI complication by primary VF is more extensive.

However, looking at large infarctions, as estimated by markedly elevated serum enzyme levels, we still observe (Table IV) an approximate twofold mortality associated with primary VF. Given that the occurrence of primary VF and its outcome are not influenced by thrombolysis, ¹⁷ the extent of necrosis does not appear to provide a satisfactory explanation of excess mortality in the group with primary VF. In the latter group, we also did not observe an increase of deaths due to pump failure. These results are dissimilar to the observations of Volpi et al.²

The major question relating to the mechanism of excess mortality found in patients with primary VF complicating AMI remains unresolved. No clinical trial could definitely determine whether primary VF was a marker for patients at increased risk of death or, alternatively, VF increased the extent of the necrosis in the myocardium by a sudden decrease in coronary flow, thus acting as an independent prognostic factor.

In our study most of the patients who died instantaneously or during recurrent arrhythmias had chest pain with concomitant ischemic electrocardiographic changes, suggesting that primary VF becomes intractable when occurring during an extension of the ischemic process.

Finally, although the in-hospital prognosis of patients with primary VF in AMI is clearly compromised, data from different studies indicate that these lifethreatening arrhythmias did not interfere with the late prognosis of the hospital survivors of AMI.2,11,18 Our own data showed comparable mortality in patients resuscitated from primary VF and in control subjects in a prolonged follow-up period over an average 5.5 years.

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APPENDIX

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Usefulness of Labetalol in Chronic Atrial Fibrillation

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Beta-adrenergic blocking agents are useful in controlling excessive ventricular rate in chronic atrial fibrillation (AF) but often reduce exercise capacity. To investigate the advantage of labetalol—a unique β blocker with α -blocking property—in chronic AF, 10 patients without underlying structural heart disease were studied with treadmill test, 12-minute walk and 24-hour ambulatory electrocardiographic monitoring. Patients were randomized and crossed over to receive 4 phases of treatment (placebo, digoxin, digoxin with half-dose labetalol, and full-dose labetalol). Exercise durations were 14.1 \pm 1.5, 14.2 \pm 1.5, 16.1 \pm 1.1 and 15.6 ± 1.1 minutes, respectively, indicating that labetalol did not reduce exercise tolerance. Although digoxin had no advantage over placebo in controlling maximal heart rate (177 \pm 2 vs 175 \pm 3 beats/ min), labetalol, both as monotherapy or as an adjunct to digoxin, was advantageous (156 \pm 4 vs 177 \pm 2 beats/min, p <0.01, and 154 \pm 4 vs 177 \pm 2 beats/min, p <0.01, respectively). The ratepressure product was consistently lowered by labetalol at rest and during exercise. At peak exercise, the addition of labetalol to digoxin reduced the maximal rate-pressure product achieved from $30,900 \pm 1300$ to 24,100 \pm 2,000 mm Hg/min (p <0.01) and the maximal rate-pressure product was lowest with full-dose labetalol (22,300 \pm 1,600 mm Hg/min). During submaximal exercise on treadmill or during the 12-minute walk, the combination of labetalol and digoxin produced the best heart rate control, whereas labetalol monotherapy was comparable to digoxin therapy. During daily activities, digoxin failed to control the maximal ventricular rate (172 \pm 5 vs 174 \pm 7 beats/min with placebo) but the addition of labetalol was efficacious (141 \pm 5 vs 172 \pm 5 beats/min; p <0.01). No bradycardia was recorded during labetalol treatment. Thus, labetalol improves heart rate control in chronic AF without decreasing exercise tolerance.

igoxin has traditionally been the drug of choice in chronic atrial fibrillation (AF)1 but its effect is limited during exercise and other stress.²⁻¹⁰ The addition of a β blocker has been recommended⁶⁻⁹ but its negative inotropic effect often diminishes exercise capacity.9-11 Labetalol, with its unique property of combined α and β blockade, has a theoretical advantage of reducing myocardial work during exercise both by controlling the ventricular rate and by reducing afterload. Similar beneficial effects have been reported in patients with hypertension, coronary artery disease and congestive cardiomyopathy. 12-18 Most previous studies of the effect of drugs on chronic AF were performed on a heterogeneous patient population with different underlying heart diseases, 1-11,19-22 which altered the cardiac responses during exercise.²³ Thus, the reported difference in the efficacy of various therapeutic strategies in chronic AF could be related to the difference in patient selection. In this study labetalol was evaluated in a homogeneous group of patients without structural cardiac abnormalities. The goal was to compare the efficacy of labetalol, in full dose or as an adjunct to digoxin, with placebo and digoxin monotherapy in chronic AF.

METHODS

Patients: Eleven stable patients (9 men, 2 women; mean age \pm standard error of the mean 55 \pm 8 years) with chronic AF were included in the study. Except for 2 patients who had controlled systemic hypertension (1 receiving thiazide and 1 nifedipine therapy), all patients had normal cardiovascular systems. In particular, no patient had evidence of Wolff-Parkinson-White or sick sinus syndrome. All patients had been maintained on digoxin alone (0.25 mg/day) for treatment of AF for ≥12 months. The serum digoxin level was determined before entry and was considered therapeutic (1.1 \pm 0.4 ng/ml). No patients had other major medical problems, such as obstructive airway disease, renal failure, Raynaud's phenomenon and alcoholism. All patients gave informed consent to the study.

Study design: After enrollment, the patients were maintained on their usual treatment and entered a phase of dose titration for 2 to 3 weeks. Labetalol was given openly from a starting dose of 100 mg twice daily to a maximum dose of 400 mg twice daily, and the dosages of the original antihypertensive drugs in the 2 patients were kept constant. Patients were then randomized and crossed over to receive all of the following 4 phases of treatment in a random sequence, with 10 to 14 days on each phase, in a double-blind fashion: (1)

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TABLE I Results of Treadmill Exercise Tests

	Placebo	Digoxin	Digoxin and Labetalol	Labetalol
Ex. time (min)	14.1 ± 1.5	14.2 ± 1.5	16.1 ± 1.1	15.6 ± 1.1
Resting HR (beats/min)	93±5	81 ± 5	74±4	82±3
Peak Ex. HR (beats/min)	175±3	177 ± 2	154 ± 4*†	156 ± 4*†
Resting SBP (mm Hg)	138 ± 10	139 ± 8	121 ± 10 ^{‡§}	117 ± 7*†
Peak Ex. SBP (mm Hg)	170±9	175±7	155 ± 10 ^{‡§}	142 ± 8‡§
Resting RPP (mm Hg/min)	$13,000 \pm 1,300$	$11,300 \pm 1,100$	9.000 ± 1.000*§	9,700 ± 900*
Peak Ex. RPP (mm Hg/min)	$29,600 \pm 1,700$	30.900 ± 1.300	24.100 ± 2.000*†	22,300 ± 1,600*†

^{*} p <0.01 when compared to placebo; † p <0.01 when compared to digoxin; † p <0.05 when compared to placebo; § p <0.05 when compared to digoxin. There was no significant fiference between the labetalol group, and the labetalol and digoxin group.

Ex. = exercise; HR = heart rate; RPP = rate-pressure product; SBP = systolic blood pressure.

Values are mean ± standard error of the mean.

TABLE II Heart Rate Response (beats/min) and Work (METS) During Treadmill Exercise and Recovery Period

And the second s					
	Placebo	Digoxin	Digoxin and Labetalol	Labetalol	Work
Before exercise	93±5	81 ± 5	74±4	82±3	0
6 minutes	119±6	106 ± 5	98±5	106 ± 5	3
12 minutes	135 ± 7	134±6	112 ± 5*	121 ± 6	7
Peak exercise	175±3	177 ± 2	$154 \pm 4^{\dagger \ddagger}$	156 ± 4 ^{†‡}	10
1-minute recovery	139 ± 5	138±6	117 ± 7 ^{†‡}	128±5	0
2-minute recovery	113±5	112±5	104 ± 4	112±3	0

^{*} p <0.05 when compared to placebo; † p <0.01 when compared to placebo; † p <0.01 when compared to digoxin. There was no significant difference between the labetalol group, and the labetalol and digoxin group. The work level at peak exercise represented the mean maximal work level achieved by all patients. Values are mean \pm standard error of the mean.

placebo, (2) digoxin in their usual dosage (0.25 mg/ day), (3) digoxin (0.25 mg/day) with half-dose labetalol (half the maximum dose tolerated in the titration phase), and (4) full-dose labetalol.

Assessment with treadmill exercise test, 12-minute walk and 24-hour ambulatory electrocardiographic recording was performed at the end of each phase of treatment.

Testing procedure: All patients were initially familiarized with maximal exercise on the treadmill (Marquette Case, Marquette Electronics Inc.). Symptomlimited exercise test using the modified Bruce protocol, which started at a work level of 2 METs, was performed in the postabsorptive state. Blood pressure was measured with a sphygmomanometer and ventricular rate was determined by the number of QRS complexes in 30 seconds on the electrocardiographic recording. These measurements were taken before exercise, in the last 30 seconds of each stage of exercise until peak exercise, and in the first, second and fifth minute of recovery. Twenty-four-hour ambulatory electrocardiographic recordings were obtained after exercise tests and the patients returned to their normal daily routines. The next day, while still on the monitor, they took a 12-minute walk in an enclosed corridor under the supervision of a physician.

Statistical analysis: Multiple paired comparisons were made for the heart rate, blood pressure and ratepressure product at each stage of the treadmill exercise test; for the maximal, minimal and average heart rate

TABLE III Systolic Blood Pressure Response (mm Hg) and Work (METS) During Treadmill Exercise and Recovery

			Digoxin and			
	Placebo	Digoxin	Labetalol	Labetalol	Work	
Before exercise	138 ± 10	139±8	121 ± 10*	117 ± 7 ^{†‡}	0	
6 minutes	153 ± 10	152 ± 10	132±11*§	117 ± 7 ^{†‡}	3	
12 minutes	154 ± 12	164±9	$137 \pm 12^{\dagger \ddagger}$	127 ± 9*‡	7	
Peak exercise	170±9	175±7	155 ± 10*§	142±8*§	10	
1-minute recovery	166±8	176±8	159 ± 9§	145 ± 7*	0	
2-minute recovery	159±8	167±7	154±9	144±7	0	

^{*} p <0.05 when compared to placebo; † p <0.01 when compared to placebo; † p <0.01 when compared to digoxin; § p <0.05 when compared to digoxin. There was no significant difference between the labetalol group and the labetalol and digoxin

during daytime activities and during sleep as recorded on the ambulatory monitor; and for the heart rate before, in the first minute of and its mean rate during the 12-minute walk. Data were paired between the 4 phases of treatment and were analyzed using the modified Bonferroni procedure.²⁴ All results were presented as mean ± standard error of the mean. A p value <0.05 after Bonferroni correction was considered statistically significant.

RESULTS

One patient did not tolerate labetalol because of postural dizziness; 10 patients completed the study. Two patients tolerated only a maximum dose of 200 mg twice daily, whereas 8 tolerated 400 mg twice daily.

Treadmill exercise performance: All patients stopped exercise because of dyspnea and fatigue. One patient had a short exercise time (<8 minutes), whereas the other 9 all tolerated ≥13 minutes. Data on this 1 patient were thus used in the analysis of exercise time. resting and peak exercise parameters but not in the analysis of submaximal exercise parameters. Labetalol was not only superior to digoxin in controlling peak exercise heart rate, but also appeared to enhance exercise tolerance (Table I). With submaximal exercise, labetalol monotherapy was comparable to digoxin in heart rate control and appeared more efficacious than did digoxin with more strenuous exercise (Table II). Systolic

The work level at peak exercise represented the mean maximal work level

achieved by all patients.

Values are mean ± standard error of the mean.

TABLE IV Rate-Pressure Product (mm Hg/min) and Work (METS) During Treadmill Exercise and Recovery

	Placebo	Digoxin	Digoxin and Labetalol	Labetalol	Work
Before exercise	13,000 ± 1,300	11,300 ± 1,100	9,000 ± 1,000*†	9,700 ± 900‡	0
6 minutes	$18,600 \pm 2,100$	16,400 ± 1,700	12,800 ± 1,200*†	12,800 ± 1,300*	3
12 minutes	$21,300 \pm 2,500$	22,400 ± 2,000	15,600 ± 1,800 ^{‡§}	15.800 ± 1.900*†	7
Peak exercise	$29,600 \pm 1,700$	30.900 ± 1.300	24.100 ± 2.000 ^{‡§}	22,300 ± 1,600 ^{‡§}	10
1-minute recovery	23,100 ± 1,700	$24,400 \pm 1,700$	19,000 ± 1,700 ^{‡§}	18.700 ± 1.500 [†]	0
2-minute recovery	18.100 ± 1.500	18.800 ± 1.400	15.900 ± 1.000	16.100 ± 1.000	

^{*} p <0.05 when compared to placebo; †p <0.05 when compared to digoxin; †p <0.01 when compared to placebo; \$p <0.01 when compared to digoxin. There was no significant difference between the labetalol group and the labetalol and digoxin group.

The work level at peak exercise represented the mean maximal work level achieved by all patients.

TABLE V Results of Heart Rate Variation (beats/min) on 24-Hour Ambulatory Electrocardiographic Recording

	Placebo	Digoxin	Digoxin and Labetalol	Labetalol
Maximal HR	174±7	172±5	141 ± 5*†	153 ± 8
Minimal HR	62±3	53 ± 4	51 ± 4	62±4
Average rate during work	102 ± 5	91 ± 4	90±5	91 ± 4
Average rate during sleep	73±3	65 ± 3‡	64±3	71±3

^{*} p <0.01 when compared to placebo; † p <0.01 when compared to digoxin. There was no significant difference between the labetalol group and the labetalol and digoxin group.

Values are mean ± standard error of the mean.
Abbreviations as in Table I.

blood pressure (Table III) and rate-pressure product (Table IV) were both reduced by labetalol.

Twenty-four-hour ambulatory electrocardiographic recording: The addition of labetalol to digoxin provided the best control of the maximal heart rate (Table V). Labetalol did not cause bradycardia.

Twelve-minute walk: The only significant finding was of a reduced heart rate before the walk, with the combination of labetalol and digoxin, although both the first minute and mean heart rates during walking tended to be lower with this combination therapy.

DISCUSSION

Previous studies of drug treatment in patients with chronic AF were performed in patients with a variety of different underlying cardiac lesions. 1-11,19-22 Whereas a higher ventricular rate during exercise in patients with lone AF can compensate for the loss of synchronized atrial contraction,23 a similar ventricular response in patients with underlying mitral stenosis or ischemic heart disease is dangerous. Because differences in patient selection can obscure the effects of drug treatment, the homogeneous group of patients without structural heart disease in this study uniquely reveals the efficacy of labetalol on the arrhythmia itself.

Our results agree with previously reported data²⁻¹⁰ on the poor efficacy of digoxin in controlling heart rate during maximal exercise and stressful life events, as reflected by the maximal recorded heart rate on the ambulatory recordings. This limitation to the efficacy of digoxin has been related to its cholinergic mechanism

on atrioventricular conduction, which is overwhelmed by sympathetic discharges during stress or vigorous exercise. 4,5 The addition of a β blocker is theoretically appropriate but previous studies have demonstrated a reduced exercise capacity with β blocker therapy. 9-11

In this study, labetalol appears advantageous, with improved heart rate control and preserved exercise capacity. Although not reaching statistical significance, the exercise time is longer with labetalol. Previous studies on the use of labetalol in essential hypertension, coronary artery disease and congestive cardiomyopathy^{12,16-18} reported improved exercise capacity, and it appeared that labetalol, through its unique combined a and β blockade properties, exerted favorable effects on both the ventricular rate and on peripheral vascular resistance, leading to a reduced rate-pressure product without compromising cardiac output. 12,16-18 Other studies on the hemodynamic effects of oral or intravenous labetalol that used invasive and noninvasive methods also reported a preserved cardiac output with reduction in blood pressure. 25-27 This contrasts with the effect of β blockers, which increase peripheral resistance and reduce cardiac output.

Our observations in patients with chronic AF are similar to those of previous studies.25-27 Rate-pressure product is reduced from rest and submaximal increased to maximal exercise with labetalol. This is contributed to by both a well-controlled ventricular rate and a reduced systolic pressure. As the rate-pressure product provides an index of myocardial oxygen consumption²⁸ and, in patients with coronary artery disease, a marker of onset of angina and ischemic electrocardiographic changes, 29,30 a reduced rate-pressure product during exercise should be advantageous, especially in patients with myocardial or coronary artery diseases.

We have not found undue bradycardia on ambulatory recordings of our patients after administration of labetalol. In previous reports studying labetalol in hypertensive patients, resting heart rate was also unaltered.31 The dosage used in this study was moderate³¹ and, as with other β blockers, 1 patient did not tolerate treatment. This experience is consistent with previously reported data on the use of labetalol in general practice in which there is a withdrawal rate of 5 to 10%.31

Clinical implications: Digoxin is ineffective in controlling ventricular response during stress or vigorous exercise. Labetalol can be a useful adjunct for achieving

Values are mean ± standard error of the mean

heart rate control without sacrificing exercise capacity. For patients with chronic AF who tolerate labetalol, the drug is a good alternative to digoxin. This especially applies to patients with underlying systemic hypertension or coronary artery disease, when a reduced rate-pressure product at rest and during exercise is particularly beneficial.

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Usefulness of Combined Propranolol and Verapamil for Evaluation of Surgical Ablation of **Accessory Atrioventricular Connections in Patients Without Structural Heart Disease**

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Successful surgical ablation of atrioventricular (AV) accessory connections may be confirmed during postoperative electrophysiologic testing by the absence of accessory connection conduction in both the anterograde and retrograde directions. Whereas the former may be readily apparent by examination of the surface electrocardiogram during sinus rhythm or atrial pacing, assessment of the latter may be complicated by the frequent presence of enhanced retrograde AV nodal conduction in the postoperative period. Consequently, availability of interventions that selectively affect AV nodal conduction and refractoriness without concomitant effects on accessory connections may be helpful for assessing the success of the surgical procedure. In this study the effects of combined propranolol and verapamil administration on electrophysiologic properties of the AV node and the accessory AV connection were assessed both pre- and postoperatively in 17 patients (12 men and 5 women, mean age 33 years) undergoing surgical ablation of accessory connections. Preoperatively, electrophysiologic characteristics of all but 1 of the accessory AV connections were unaffected by propranolol and verapamil administration. Postoperatively, on the other hand, propranolol and verapamil significantly prolonged both the retrograde AV node effective refractory period (baseline: 272 \pm 34 ms vs after drugs: 384 \pm 70 ms [p <0.0001]) and the shortest cycle length maintaining 1:1 ventriculoatrial conduction (baseline: 357 \pm 99 ms vs after drugs: 485 \pm 64 ms [p <0.0001]). Late postoperative electrophysiologic evaluation (7 ± 3 weeks) revealed no evidence of residual accessory AV con-

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nection conduction, and all patients remain asymptomatic at 21 \pm 10 months follow-up. Thus, the combined administration of propranolol and verapamil may prove helpful for differentiating between retrograde AV nodal and residual accessory connection conduction during early postoperative assessment of patients undergoing surgery for accessory AV connection ablation.

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The success of surgical ablation of accessory atrioventricular (AV) connections may be confirmed during postoperative electrophysiologic evaluation by establishing the absence of ventricular preexcitation, when it had been present preoperatively, by demonstrating ventriculoatrial dissociation, or both. The former may be evident by examination of the surface electrocardiogram during sinus rhythm and atrial pacing, but alone does not exclude the presence of an accessory AV connection that conducts only in the retrograde direction. Consequently, demonstration of ventriculoatrial dissociation during ventricular pacing is an integral part of the postoperative assessment of the effectiveness of surgery. However, in the early postoperative period, many patients may exhibit excellent ventriculoatrial conduction due to the effects of catecholamines or as a result of concomitant enhanced retrograde AV nodal conduction. In some of these cases, the sequence of atrial activation during ventricular pacing may help to differentiate conduction through a residual accessory AV connection or the AV node, but this approach requires a multicatheter study and may be equivocal for septal accessory AV connections. On the other hand, maneuvers that selectively affect AV nodal conduction characteristics, without concomitant effects on the accessory AV connection, may be helpful in the immediate postoperative period for confirming the success of the surgical procedure.

Propranolol and verapamil have profound negative dromotropic effects on the AV node, and are not generally believed to exert direct effects on conduction over accessory AV connections. Thus, these agents may be useful for elucidating the nature of ventriculoatrial conduction in patients who have recently undergone an at-

Patient	SCL	PA	AH	HV	AVERP	ACERP	AVRERP	ACRERE
				No Drugs				
1	730	50	60	55	310			250
2	950	50	60	40	390	_	_	290
3	900	40	50	15	-	230	-	300
4	840	35	90	40	260	-	-	240
5	760	50	60	10	230	240		230
6	710	60	75	45	250	_	_	240
7	740	65	60	20	_	260	-	250
8	730	35	40	0	240	290	-	240
9	760	35	40	25	-	240	-	220
10	850	40	45	0	250	260	260	320
11	820	40	60	10		240		230
12	610	40	50	15	-	240		220
13	820	50	65	25	280	360		280
14	920	50	50	20	220	380		320
15	850	40	70	40	260	-	_	290
16	610	30	60	0	250	280	240	280
17	630	25	65	25	210	500	230	260
Mean ± SD	778 ± 104	43 ± 10	59 ± 13	23 ± 17	263 ± 48	293 ± 81	243 ± 15	262 ± 3
			Proprano	lol and Verapar	nil			
1	850	50	85	55	370	WINTER	ME LES	250
2	1150	50	75	40	430	_		290
3	1100	40	65	0	_	230		300
4	920	40	120	40	360			320
5	810	50	70	0	_	240	-	230
6	800	60	90	45	320	_	-	240
7	840	65	80	0	_	260	_	250
8	850	40	65	0	_	290		240
9	820	35	65	15		240		220
10	1000	40	70	0		260	_	320
11	900	40	75	0	5_1 A	240	-	220
12	660	40	80	0		240		220
13	980	50	90	0	340	360		280
14	1100	50	85	0	270	380	100 <u>100</u> 100 100 100 100 100 100 100 100 100	320
15	900	50	95	40	340	_	-	280
16	650	30	75	0		280	-	280
17	750	35	90	0	270	500	- <u> </u>	260
Mean ± SD	887 ± 144	45±9	81 ± 14	14±21	338 ± 53	293 ± 81		266±3

tempted ablation of an accessory AV connection, thereby distinguishing whether successful ablation of an accessory AV connection had been achieved. To this end, we compared the effects of these drugs both preoperatively and postoperatively on electrophysiologic properties of the AV node and the accessory AV connection in 17 patients undergoing surgical ablation of accessory AV connections.

METHODS

Patient group: Seventeen patients referred to the Clinical Electrophysiology Laboratory of the University of Minnesota Hospital for surgical ablation of accessory AV connections form the basis for this report. Exclusion criteria included left ventricular dysfunction of sufficient severity to contraindicate combined propranolol and verapamil administration, bronchial asthma, diabetes mellitus or known or suspected history of adverse reaction to propranolol or verapamil. All patients underwent complete medical history and physical examination, 12-lead electrocardiogram, chest roentgenogram, echocardiogram, and electrophysiologic studies before and after a surgical procedure to ablate the accessory AV connection(s). Patients >40 years also underwent coronary angiography before surgery.

Electrophysiologic studies: PREOPERATIVE ELECTRO-PHYSIOLOGIC STUDY: Patients were studied in the postabsorptive state, ≥72 hours after discontinuation of all antiarrhythmic drugs. Quadripolar electrode catheters were positioned in the high right atrium, right ventricular apex and coronary sinus, and across the tricuspid valve for His bundle recording. Standard methodology for intracardiac recordings and programmed stimulation were used to determine the electrophysiologic properties of the normal AV conduction system and the accessory AV connection.2 Extrastimulus testing for determination of atrial and ventricular effective refractory periods (ERPs) were undertaken at 2 basic pacing cycle lengths (600 and 400 ms). Incremental pacing to the point of AV and ventriculoatrial block were performed from the high right atrium and right ventricular apex, respectively. Upon completion of baseline study, patients were administered intravenous propranolol, 0.02 to 0.05 mg/kg, followed by intravenous verapamil, 0.10

to 0.15 mg/kg. Programmed stimulation was repeated beginning approximately 10 minutes later, with all studies completed within 30 minutes of drug administration.

POSTOPERATIVE ELECTROPHYSIOLOGIC STUDY: Electrophysiologic evaluation was performed immediately after surgery, 24 hours postoperatively, 5 to 7 days postoperatively and 6 to 8 weeks postoperatively. In the first week after surgery, studies were performed in the absence of antiarrhythmic medications using epicardial electrodes sutured to the right atrial appendage and anterior right ventricle. Atrial and ventricular extrastimulus testing was performed at cycle lengths comparable to those used in the preoperative study. Atrial and ventricular incremental pacing was similarly performed to assess anterograde and retrograde conduction. All studies were then repeated 10 minutes after combined intravenous administration of propranolol and verapamil (doses as in preoperative studies). The methodology of the 6 to 8

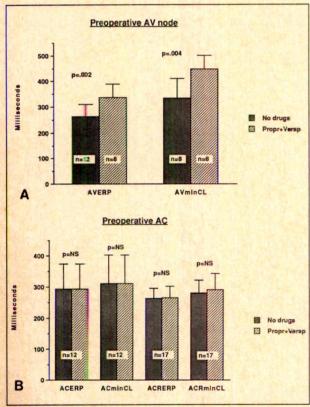


FIGURE 1. A, histograms depicting effects of combined propranolol (Propr) and verapamil (Verap) administration on prolongation of both anterograde atrioventricular (AV) nodal effective refractory period (ERP) and the shortest cycle length maintaining 1:1 anterograde conduction over the AV node during preoperative evaluation. B, histograms summarizing effects of propranolol and verapamil on anterograde and retrograde accessory connection ERP and shortest cycle length maintaining 1:1 conduction during preoperative evaluation. AVERP = anterograde AV node ERP; AVminCL = shortest cycle length maintaining 1:1 anterograde conduction over the AV node; ACERP = anterograde accessory connection ERP; ACminCL = shortest cycle length maintaining 1:1 anterograde conduction over the accessory connection; ACRERP = retrograde accessory connection ERP; ACRminCL = shortest cycle length maintaining 1:1 retrograde conduction over the accessory connection.

weeks postoperative electrophysiologic assessment was similar to that used during preoperative electrophysiologic evaluation. However, we do not routinely use a coronary sinus catheter during postoperative electrophysiologic evaluation unless specifically indicated by the electrophysiologic findings, and none was required in this group of patients.

Definitions: Previously published standard definitions for ERP measurements as well as shortest cycle length maintaining 1:1 conduction over the AV node and the accessory AV connection were used in this study.2

Data analysis: Electrophysiologic properties of the AV node and accessory AV connections were compared before and after propranolol and verapamil administration in each study. For statistical purposes the postoperative data used were those obtained during the 24-hour postoperative electrophysiologic assessment. In patients with multiple accessory AV connections, the connection with the shortest ERP was analyzed. Refractory periods obtained at a basic drive cycle length of 400 ms were used for comparison. The Student t test for paired or

Patient	SCL	AVERP	AVRERP
Revolution in	No Drug	gs	
1	620	300	340
2	860	330	270
3	690	260	340
4	770	240	250
5	650	240	250
6	620	250	270
7	710	260	VAD
8	730	270	230
9	700	260	230
10	820	230	280
11	750	250	260
12	640	280	270
13	750	250	310
14	900	365	VAD
15	770	240	280
16	620	270	250
17	650	240	250
Mean ± SD	721 ± 85	267 ± 35	272 ± 34
	Propranolol and	Verapamil	el amanda
1	740	390	VAD
2	920	370	430
3	720	350	410
4	850	390	560
5	820	330	320
6	750	340	360
7	780	340	VAD
8	790	350	320
9	820	320	310
10	860	320	340
11	800	310	370
12	720	380	410
13	820	310	370
14	770	340	VAD
15	900	320	390
16	690	420	470
17	710	290	310
Mean ± SD	792 ± 67	345 ± 35	384 ± 70

unpaired observations, as appropriate, was used to assess the statistical significance of differences between electrophysiologic measurements obtained in the baseline state and after propranolol-verapamil administration. A p value <0.05 was considered significant.

RESULTS

Patients: Seventeen patients, 12 men and 5 women, ages 9 to 61 years (mean \pm standard deviation 33 ± 16) were included in this study. In all patients there was no evidence of structural heart disease.

Preoperative electrophysiologic study: Seventeen patients had 19 accessory AV connections; 15 accessory AV connections were bidirectional and 4 conducted only in the retrograde direction ("concealed"). In 2 patients who had 2 accessory AV connections each (patients 9 and 17) only the connection with the shortest ERP was analyzed. One of the bidirectional accessory AV connections manifested only intermittent ventricular preexcitation and is included in the study as a concealed accessory AV connection. Consequently, the effects of propranolol and verapamil were assessed in patients having 12 accessory AV connections with anterograde conduction and 17 with retrograde conduction. Ten accessory connections crossed the AV groove in the left ventricular free wall region, 4 were in the posteroseptal region, 2 were along the right ventricular free wall and 1 was in the anteroseptal region.

Table I summarizes basic conduction intervals and refractory periods of the AV node and accessory AV connections before and after propranolol and verapamil administration during the preoperative electrophysiologic study. Figure 1A shows a comparison of AV nodal anterograde refractoriness before and after pharmacologic intervention in the preoperative evaluation, whereas Figure 1B depicts accessory AV connection refractoriness in the same setting. Baseline (drug-free) evaluation of retrograde AV nodal conduction and refractoriness could only be obtained in 3 patients (patients 10, 16 and 17), because the ERPs of the accessory AV connections were shorter than those of the AV

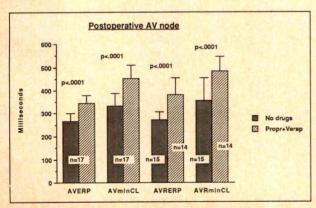


FIGURE 2. Histograms illustrating the effects of propranolol and verapamil on anterograde and retrograde AV nodal refractoriness during postoperative evaluation. AVRERP = retrograde AV node ERP; AVRminCL = shortest cycle length maintaining 1:1 retrograde conduction over the AV node; other abbreviations as in Figure 1.

node in 14 of the 17 patients. However, among these 3 patients, retrograde AV nodal conduction and refractoriness could not be evaluated after propranolol and verapamil administration because AV node refractoriness prolonged beyond accessory connection refractoriness. Not unexpectedly, propranolol and verapamil significantly prolonged AV nodal conduction time and refractoriness in all patients in whom AV nodal electrophysiologic properties could be evaluated (Table I). Conversely, in all but 1 patient (patient 4), electrophysiologic properties of accessory AV connections were unaffected by combined pharmacologic effects of propranolol and verapamil (Table I). In this case the accessory AV connection was a concealed left free wall accessory AV connection in which the retrograde effective refractory period was prolonged from 240 to 320 ms after drug infusion.

Postoperative electrophysiologic study: Two patients (patients 7 and 14) had ventriculoatrial dissocia-

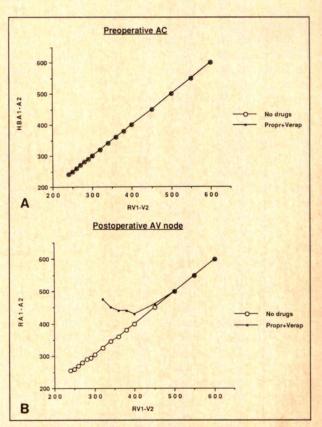


FIGURE 3. A, graph depicting the effects of propranolol and verapamil administration during right ventricular extrastimulus testing in the preoperative evaluation of patient 8. Note the superimposed V_1 to V_2 versus A_1 to A_2 curves before (open circles) and after (dots) propranolol-verapamil administration. A_1 to A_2 measurements illustrated are those from the His bundle (HB) recording site. B, postoperative assessment of ventriculoatrial conduction during right ventricular extrastimulus testing in patient 8. Curves resulting from plotting V_1 to V_2 versus A_1 to A_2 intervals (from the right atrial recording site) before and after propranolol-verapamil administration differ markedly. The curve obtained before drugs (open circles) is nearly identical to the accessory atrioventricular connection curve in A. RA = right atrial recording site; other abbreviations as in Figure 1.

tion at all testable ventricular paced rates immediately after surgery, and consequently the effects of propranolol and verapamil could not be evaluated. Additionally, 1 patient (patient 1) developed ventriculoatrial dissociation after the drugs were administered and findings in this patient could not be used for statistical comparison. Consequently, effects of propranolol and verapamil on AV nodal conduction characteristics were evaluated in the anterograde direction in 17 patients and in the retrograde direction in 14 patients (Table II).

Eleven patients had a retrograde AV node ERP of <300 ms, and it was in this group of patients that drug testing proved particularly useful. Figure 2 shows AV node ERP measurements before and after drug infusion in the postoperative evaluation. Propranolol and verapamil significantly prolonged both the retrograde AV node ERP, and the shortest cycle length maintaining 1:1 retrograde AV nodal conduction (Table II). Differences in response to propranolol and verapamil before and after surgery (comparison of Figures 1B and 2) implies successful accessory AV connection ablation and retrograde conduction over the AV node.

Follow-up: Late postoperative evaluation (7 ± 3) weeks) revealed a lack of inducible reciprocating tachycardia and no evidence of residual accessory AV connection conduction. Further, all patients have remained asymptomatic from an arrhythmic point of view during a 21-month (± 10) follow-up period.

DISCUSSION

Findings in this study demonstrate that the combined pharmacologic effects of propranolol and verapamil do not significantly alter electrophysiologic properties of accessory AV connections in the majority of patients undergoing accessory AV connection surgical ablation, whereas they do slow conduction and prolong refractoriness of the AV node in both the anterograde and retrograde direction in these same patients. Consequently, these observations provide a rationale for the use of combined propranolol and verapamil administration as an aid for differentiating conduction over residual accessory AV connection tissue from enhanced retrograde AV nodal conduction in the postoperative assessment of patients undergoing surgical ablation of accessory AV connections.

Effects of propranolol and verapamil on the atrioventricular node: Propranolol has a negative dromotropic effect on the AV node as a result of competitive binding to β-adrenergic receptor sites.³ Verapamil, a calcium channel inhibitor, similarly exhibits a well recognized negative dromotropic effect on the AV node, but it also reduces systemic vascular resistance through its effects on vascular smooth muscle.⁴ The latter effect may result in reflex sympathetic discharge that may indirectly counteract verapamil's direct negative dromotropic effect on the AV node. Consequently, an additive effect of propranolol and verapamil on AV nodal depression of conduction and refractoriness is to be expected, and indeed was previously demonstrated by Yee et al.⁵

Effects of propranolol and verapamil on accessory atrioventricular connections: Previous reports detailing the use of combined β -adrenergic blockers and calcium antagonist drugs in patients with accessory connections suggest that only a minority of accessory connections (<10%) are affected by these agents. Yeh et al⁶ evaluated effects of a single oral dose of diltiazem and propranolol in 15 patients with recurrent paroxysmal supraventricular tachycardia. In 13 of these patients an accessory AV connection was part of the reentrant circuit. None of the accessory connections had a significant drug-induced change in anterograde or retrograde electrophysiologic properties. Conversely, in 2 patients with AV nodal reciprocating tachycardia (one with "fast-slow" and the other with "slow-fast" AV nodal reentry), diltiazem and propranolol resulted in significant prolongation of retrograde refractoriness and ventriculoatrial dissociation, respectively. Harper et al7 studied the effects of verapamil in 12 patients with Wolff-Parkinson-White syndrome. They found that verapamil did not affect the anterograde or retrograde effective refractory period of the accessory connection, but prolonged by up to 10% the shortest cycle length maintaining 1:1 conduction over the accessory AV connection in the anterograde direction in some patients. Nonetheless, a 10% prolongation in the shortest cycle length maintaining 1:1 conduction over the accessory connection is much less than the 30% prolongation of shortest cycle length maintaining 1:1 conduction over the AV node demonstrated in this study (Figure 1A). In addition, the test is not as important for assessing conduction in the anterograde direction (where ventricular preexcitation is usually obvious) as it is for evaluating conduction in the retrograde direction, where enhanced AV nodal conduction may be otherwise almost impossible to differentiate from conduction over a residual accessory connection (Figure 3).

Yee et al⁵ studied the effects of combined propranolol and verapamil in 14 patients with paroxysmal supraventricular tachycardia. While the drugs affected anterograde and retrograde AV nodal conduction and refractoriness in 4 patients with AV nodal reciprocating tachycardia, they did not affect anterograde or retrograde conduction and refractoriness in 9 patients with conventional accessory connections, and affected retrograde conduction in only 1 patient with an AV node-like accessory connection.

Study limitations: Interpretation of the results of this study is subject to limitations. First, the use of verapamil to differentiate AV node from accessory connection conduction relies on a relative absence of calcium channel antagonist effects on accessory AV connections. However, Tai et al⁸ reported both direct and indirect effects of verapamil in 5 of 31 patients with accessory connections. In 3 patients the effect of verapamil on the accessory connection was due to functional block secondary to alternating fast-slow conduction over the AV node. In 2 other patients there was evidence for direct verapamil-induced impairment on accessory connection conduction and refractoriness. In 1 of our patients with

a left free wall accessory connection, combined propranolol-verapamil administration during preoperative electrophysiologic study revealed a similar effect, manifested by prolongation of conduction and refractoriness in the accessory connection. This example highlights the importance of a thorough preoperative evaluation of the effects of the drugs on accessory connection properties as a preliminary step to their use in the postoperative assessment. Thus, if a direct negative dromotropic effect of these drugs on the accessory connection is confirmed preoperatively, they should not be used during postoperative evaluation of the success of surgery. Second, none of our patients had residual accessory AV connections in postoperative electrophysiologic studies. Consequently, the potential for prolongation of conduction and refractoriness in partially damaged but incompletely ablated accessory AV connections after drug administration cannot be unequivocally excluded. Lastly, safety of infusion of drugs with combined negative chronotropic, dromotropic and inotropic effects in the immediate postoperative period might reasonably raise concern. In our experience, only transient moderate hypotension and heart rate slowing occurred. However, our study population comprised only patients with normal sinus node and normal left ventricular function, characteristics not uncommon among patients undergoing accessory AV connection surgical ablation. Presumably, individuals with abnormal sinus node function or clincally significant left ventricular dysfunction would not be appropriate candidates for this drug combination. Ultimately, availability of short-acting drugs without deleterious hemodynamic effects, such as adenosine or adenosine triphosphate, may be helpful in these patients. 9,10

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Long-Term Effect of Mexiletine on Left Ventricular Function and Relation to Suppression of Ventricular Arrhythmia

Steven Singh, MD, Richard Klein, MD, Brian Eisenberg, MD, Edward Hughes, MD, Margaret Shand, RN, and Pat Doherty, RN, with the technical assistance of Gerhard Sharon

The effects of oral mexiletine on left ventricular (LV) ejection fraction (EF) and ventricular arrhythmias—and a possible relation between these effects-were evaluated during 3 months of therapy in 29 patients with chronic ventricular premature complexes (VPCs) and a moderately reduced to normal LVEF by 24-hour Holter monitoring and by radionuclide ventriculography at rest and during maximum tolerable exercise testing. After an average titration period of 13 days, a mean daily mexiletine dose of 739 mg was maintained throughout the treatment. At the end of titration and after 3 months of treatment, patients with a baseline LVEF ≤40% (group 2) responded with a median reduction of the hourly VPC rate by 90 and 81%, respectively, compared with 79 and 72% in those with a baseline LVEF >40% (group 1). Couplets and runs of ventricular tachycardia were almost completely suppressed in nearly all patients. A single patient had a proarrhythmic increase in VPCs during treatment. Compared with baseline, there were no significant changes in resting or exercise LVEF after 1 or 3 months of treatment in either of the 2 groups of patients. No correlation was found between treatment-induced changes in arrhythmia frequency and in resting EF. No symptoms of congestive heart failure developed. The study confirms that long-term use of mexiletine is efficacious and relatively free of cardiac depressant effects even in patients with diminished LV function.

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The treatment of ventricular arrhythmias presents serious problems in patients with depressed left ventricular (LV) function or chronic congestive heart failure because such patients tend to be less responsive to conventional antiarrhythmic drug therapy than those with normal LV function.^{1,2} Patients with LV dysfunction also appear to be more vulnerable to possible negative inotropic effects of antiarrhythmic drugs and to drug-induced aggravation of arrhythmia.^{1,3,4}

Studies with mexiletine in patients with a history of myocardial infarction, ^{5,6} LV dysfunction and congestive heart failure ⁷⁻⁹ as well as in normal subjects ¹⁰ have not shown important adverse effects of this agent on cardiovascular performance.

In the open-label 3-month study reported here, we assessed the chronic effect of oral mexiletine on LV function in patients with a normal to moderately reduced ejection fraction (EF) and examined at the same time a possible relation between this effect and the suppression of ventricular premature complexes (VPCs).

METHODS

Study design: In this study, conducted at 2 clinical centers, patients who had previously been treated with antiarrhythmic drugs first entered a placebo washout period, equaling in duration at least 5 half-lives of the drug they had taken last. For all patients, this was followed by a 3-day placebo control period designed to establish the patient's eligibility and to secure baseline readings. In both of these periods, 1 placebo capsule was administered every 8 hours.

Qualifying patients began titration to determine a tolerable and effective dose of mexiletine. The incremental doses tested were one 200-mg capsule, two 150mg capsules, and two 200-mg capsules at dosage intervals of 8 hours for total daily doses of 600, 900 and 1,200 mg. Each dose was taken for 1 week. An adequate response was considered to be a decrease of ≥70% in the hourly VPC rate (in accordance with the efficacy criterion used in the Cardiac Arrhythmia Pilot Study¹¹). Patients who had intolerable adverse reactions or who failed to show the requisite degree of arrhythmia suppression at the highest dose were withdrawn from the study. After titration, the patients entered a stabledose treatment period in which they were instructed to continue taking the same titrated dose at 8-hour intervals until 3 months had passed since the first day of mexiletine administration.

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Pt Age Heart		Structural	EF (%)		VPCs/Hou	VPCs/Hour		Couplets/Hour		VT/Hour	
No.			Baseline	Mexiletine	Baseline	Mexiletine	Baseline	Mexiletine	Baseline	Mexiletine	
13	52	CAD	27	24	187	64	4.3	0.4	0.1	0	
24	53	CAD	51	61	101	218	0.3	2.2	0	0.1	
17	58	CAD	57	38	60	8	1	0	0	0	
7	59	CAD	38	32	484	82	91	0.4	3.2	0.1	
20	59	CAD	33	36	461	7	12	0.1	3.5	0	
4	64	CAD	36	31	1027	18	452	0.9	7	0.1	
19	66	CAD	45	46	38	1	1	0	0	0	
1	67	CAD	25	25	45	1	2	0	0	0	
3	67	CAD	39	41	47	8	1	0.1	0	O	
5	67	CAD	46	53	211	54	6	0	0	0	
10	69	CAD	49	41	136	38	2	0.2	0.03	0	
11	69	CAD	26	22	187	69	2 2	0.9	0.03	0	
2	71	CAD	51	50	272	48	22	0.4	0.6	0	
12	72	CAD	38	44	193	177	7.4	2.3	0.0	2.3	
6	74	CAD	21	21	352	286	9.5	13	10	0.2	
9	74	CAD	44	51	231	109	49	10	1.0	0.2	
8	45	IDC	38	34	54	303	0	0.6	0	0.2	
18	61	SH	54	57	177	84	96	3.4	0	0	
16*	63	SH	41	41	232	129	9.5	3.4	0.4	0	
22	66	SH	79	79	275	150	0.5	0.1	0.4	0	
28*	66	SH	43	45	219	69	5.3	0.1	0.4	0	
14*	69	SH	61	66	488	97	2.2	0	0.4	0	
21	70	SH	46	65	35	10	1.8	0.1	0	0	
23	70	SH	53	51	139	48	7.7	4.6	0	0	
29	70	SH	76	64	188	183	4.8		0.2	0	
5	54	<u>-</u>	49	59	29	3		0	0	0	
5	59		49	48			0	0	0	0	
26	62		40	39	609 811	115 181	54 0.3	1.0	0.5	0	

*These patients had measurements only at 1 month or at the end of titration.

CAD = coronary artery disease; EF = left ventricular ejection fraction at rest; IDC = idiopathic dilated cardiomyopathy; SH = systemic hypertension; VPC = ventricular premature complexes; VT = ventricular tachycardia.

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Patient selection and characteristics: Patients selected for this study were between 21 and 75 years old and had chronic ventricular arrhythmias at an average VPC rate of ≥30 beats/hour, as established by two 24-hour ambulatory electrocardiographic recordings and a resting LVEF ≥25%. Patients with hypotension, atrioventricular block, supraventricular arrhythmias and acute myocardial infarction or symptoms of acute congestive heart failure within the last 6 weeks were not admissible.

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75

In all, 49 men aged 45 to 74 years (mean 64) were admitted. Twenty patients were excluded from analysis of the study results: 13 discontinued treatment prematurely because of intolerance of mexiletine (9 in the titration phase and 4 in the stable-dose phase); 3 were lost to follow-up (in titration phase); 2 were found not to meet the entrance criteria (during titration), whereas 1 patient failed to respond (in titration phase) and 1 developed a medical complication (in stable-dose phase). Thus, 29 patients were available for evaluation.

Measurements and observations: All patients had their history taken and underwent a physical examination at the beginning of the placebo washout or placebo control period. Two Holter recordings were obtained during the first 2 days of the control phase. Patient visits were scheduled once a week during the titration phase and at the end of each month of stable-dose treatment. Laboratory tests done on the first day of the placebo control period and at the end of each month of the

chronic treatment phase comprised a complete blood count and chemistry and liver profiles. An electrocardiogram recorded at the end of the control period was compared with electrocardiograms obtained at the end of each titration period and at the end of 1 and 3 months of treatment. For the arrhythmia response, a 24-hour Holter recording was obtained toward the end of each titration period and at the end of the 3-month treatment (including titration). The results of ambulatory electrocardiographic monitoring were interpreted by a third party who was blinded to the nature of the treatment.*

In this study, nonsustained ventricular tachycardia was defined as 3 to 9 consecutive ventricular complexes, and sustained ventricular tachycardia as ≥10 ventricular complexes.

The patients were further examined for symptoms and signs of congestive heart failure at the end of the placebo control period, at the end of titration, and at the end of 1, 2 and 3 months of maintenance treatment. LVEF was measured noninvasively, with the patient in sinus rhythm, both at rest and during symptom-limited maximal stress exercise by the method of multigated acquisition equilibrium blood pool scanning at the end

^{*}For quality control, 5% of all Holter recordings from this study were audited for reproducibility and accuracy. The audit covered a randomly selected period of 4 consecutive hours from each Holter recording.

TABLE II Mean Resting Left Ventricular Ejection Fractions and Mean Hourly Frequencies (with Standard Deviations) and Median Percent Reductions of Ventricular Arrhythmias

	LVEF (%)			VPCs/Ho	VPCs/Hour			Couplets/Hour			VT/Hour					
		Months				Months					- Couplets/			TT/TIOUI	Fueled	
	Baseline	1	3	Baseline	End of Titrat.	3 Months	Baseline	End of Titrat.	3 Months	Baseline	End of Titrat.	3 Months				
All patients Median % reduction	46 (14)	48 (15) —	46 (16) —	273 (248)	43 (39) 84	87 (90) 73	31 (88) —	0.6 (1.1) 98	1.6 (3.2) 97	1.8 (2.9)	0.0 (0.0) 100	0.05 (0.08) 97				
Group 1	1 1											Novie de				
Baseline	54	55	55	238	39	76	12.5	0.7	1.5	0.3	0.0	0.05				
EF > 40%	(12)	(13)	(12)	(211)	(35)	(75)	(24.6)	(1.3)	(2.8)	(0.3)	(0.0)	(0.09)				
Median % reduction	-	-	-	-	79	72	-1	96	97	-	100	83				
Group 2		Trains.					STATE OF	N. A. S.			1281					
Baseline	33	35	33	332	48	103	64	0.5	1.9	3.4	0.0	0.05				
EF ≤ 40%	(7)	(6)	(9)	(300)	(46)	(109)	(140)	(0.5)	(3.8)	(3.7)	(0.0)	(0.08)				
Median % reduction	-	-			90	81	-	99	95		100	99				

of the control period and at the end of 1 and 3 months of mexiletine therapy. The results were again interpreted by a third party blinded to the treatment.*

Methods of evaluation: The 29 patients with evaluable data were classified into 2 groups: one that had resting baseline EFs >40% (group 1, n = 18) and one in which resting LVEF at baseline was ≤40% (group 2, n

The 29 patients included 3 from whom data were available only at the end of titration or 1 month of therapy, and 1 from whom data were available only at the end of the 3-month stable-dose phase. Both 1- and 3month measurements were obtained for the remaining 25 patients. Of the 49 patients originally admitted, 48 were available for other safety evaluations; one was excluded because he was lost to follow-up before the first treatment evaluation visit.

A paired t test was used to analyze changes in LVEF between baseline and after 1 and 3 months of mexiletine treatment. Changes in LVEF produced by exercise testing after 1 and 3 months of treatment were compared with the exercise-induced changes at baseline, using the signed rank test. Inasmuch as these derived data were not normally distributed, median values are presented. In 46 patients who had a follow-up electrocardiogram to the baseline recording, mean changes in the PR, QRS and QTc intervals were evaluated.

To determine whether any aggravation of arrhythmia should be classified as a proarrhythmic effect of the drug, reference was made to the criteria for proarrhythmic effects used in the Cardiac Arrhythmia Pilot Study¹¹ to evaluate increases in VPC frequency. Assessments were made on the basis of the last Holter recording obtained after treatment compared with the baseline 24-hour recording.

Blood pressures and pulse rates recorded at each clinic visit during treatment were compared with those recorded before treatment.

RESULTS

Titration and dosage: A total of 34 patients completed the titration phase after an average of 13 days from the first mexiletine dose. Mean daily doses at the end of titration were 739 mg for all patients, whereas the mean for group 1 (LVEF >40%) was 750 mg and that for group 2 (LVEF ≤40%) 720 mg. Most patients responded to a mexiletine dose of 200 mg 3 times daily. Capsule counts showed that compliance was ≥80% in virtually all patients.

Antiarrhythmic effect and left ventricular function: The individual 29 patients' ages, diagnoses and baseline values together with end-of-treatment readings of resting EF and hourly frequencies of VPCs, couplets and ventricular tachycardia are listed in Table I. At baseline, at the end of titration and at the end of treatment. all runs of ventricular tachycardia were nonsustained except for 1 run of <50 beats that occurred at baseline in patient 10.

Mean resting LVEF values and mean and median percent changes from baseline in the hourly frequencies of VPCs, couplets and nonsustained ventricular tachycardia at the different study intervals are listed for all evaluable patients, as well as separately for each of the 2 groups, in Table II. The efficacy criterion for VPC suppression was satisfied, with some variation over the course of the study.

LVEF at rest measured in each of the 29 patients from baseline until the end of the stable-dose period is shown graphically for groups 1 and 2 in Figures 1 and 2. Mean changes from baseline were not statistically

^{*}The accuracy of these measurements was validated by periodic audits involving comparison of the results with those obtained by cardiac catheterization, echocardiography, or both.

significant. After 1 month of mexiletine therapy, mean change was a 2% increase; group 1 patients with the higher baseline EF showed a slightly smaller mean increase (1.6%) than group 2 (2.6%). At the end of the 3month treatment, changes were even smaller in both groups, averaging +0.7 and -0.3% in groups 1 and 2, respectively, and +0.3% in the 2 groups combined.

Similarly, mean EF changes from baseline at the maximum tolerable exercise level were small for all patients (a decrease from 49.0 to 46.5%) as well as in each of the 2 patient groups (-2.8% in group 1 and -3.9% in group 2) after 1 month of mexiletine therapy. After 3 months, mean change from the baseline exercise EF was only 1% in all patients. In group 1, the change from baseline was practically nil (-0.1%), whereas a mean increase of 2.2% was seen in group 2.

The effect of mexiletine treatment on the EF response to exercise is presented in Table III. After treatment, median changes with exercise were slightly more positive in group 2 than in group 1, particularly at the 1-month interval, but did not prove statistically significant when compared with the responses to exercise at

TABLE III Exercise-Induced Median Changes in Left Ventricular Ejection Fraction (LVEF) Before and After Mexiletine Treatment (Change Computed as EF at Maximal Tolerated Exercise Level Minus Resting EF)

	Baseline	Mexiletine Treatment		
		1 Month	3 Months	
All patients	(n = 29)	(n = 25)	(n = 24)	
Median change with exercise	+5.0%	+4.0%	+3.5%	
Group 1				
EF at baseline > 40%	(n = 18)	(n = 16)	(n = 13)	
Median change with exercise	+6.0%	+3.5%	+3.0%	
Group 2				
EF at baseline ≤ 40%	(n = 11)	(n = 9)	(n = 11)	
Median change with exercise	+2.0%	+7.0%	+4.0%	

baseline. Changes from the baseline responses to exercise reached statistical significance (p = 0.04) only for group 1 after 1 month of treatment, while bordering on significance (p = 0.05) for the 2 groups combined. In no case were they clinically significant, however.

FIGURE 1. Resting left ventricular ejection fraction during mexiletine treatment in each of 18 patients with a baseline ejection fraction >40% (+ = mean ejection fraction).

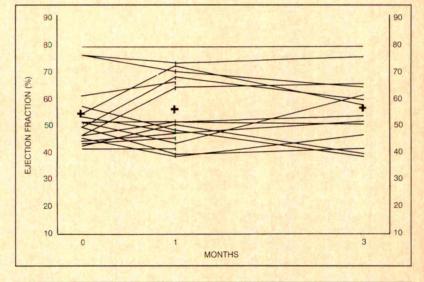
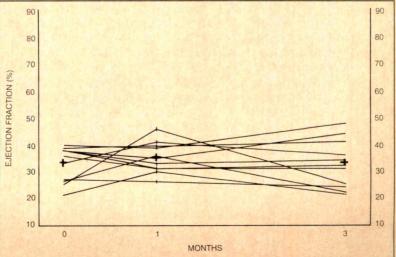


FIGURE 2. Resting left ventricular ejection fraction during mexiletine treatment in each of 11 patients with a baseline ejection fraction ≤40% (+ = mean ejection fraction).



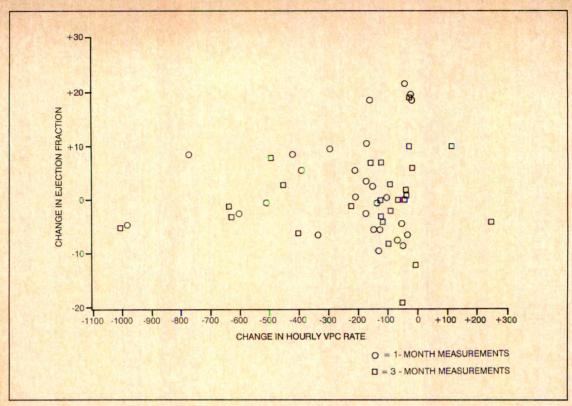


FIGURE 3. Relation between change in left ventricular ejection fraction and change in hourly ventricular premature complex (VPC) rate in each patient after 1 and 3 months of mexiletine treatment.

Another objective of our study was to determine whether changes in arrhythmia frequency in response to treatment were correlated with changes induced in LVEF. Scatter plots (Figure 3) of changes in hourly VPC rate and (resting) EF in individual patients at 1 and 3 months failed to show any relation between the individual values of these 2 parameters.

Other safety observations: In the 29 patients, mean blood pressures increased slightly in the course of the study: mean systolic blood pressure increased by 3 mm Hg and mean diastolic by 4 mm Hg. There were no appreciable changes in pulse rates.

Mean PR, QRS and QTc intervals at the end of treatment were substantially unchanged from those recorded at baseline. One patient who had cardiomyopathy and a baseline resting EF of 38% had an increase of proarrhythmic magnitude in the VPC rate after 3 months of mexiletine treatment, while ventricular tachycardia remained completely suppressed and couplet activity was almost completely absent.

Adverse experiences: Of the 49 patients originally admitted, 13 discontinued treatment because of adverse experiences probably related to mexiletine. Nine of these withdrawals occurred during titration and were occasioned by gastrointestinal complaints such as nausea, vomiting and diarrhea in 10 cases, and by central or peripheral nervous system symptoms such as dizziness, tremor and weakness in 8 cases; 5 patients had both gastrointestinal and nervous symptoms. Among the 29 patients with analyzable arrhythmia and EF data, 11 or 40% had generally mild untoward reactions that were probably drug-related, including tremor, dizziness, nau-

sea and abdominal discomfort. One of these patients withdrew from the study prematurely because of a combination of these adverse reactions.

DISCUSSION

The present study has confirmed previous observations⁷⁻⁹ based on measurements of LVEF by gated pool radionuclide ventriculography that mexiletine treatment does not significantly affect LV function in patients in whom this was moderately to markedly impaired at the time of entry into the study. The significance of EF response to exercise as a measure of the contractile reserve of the myocardium, and the usefulness of exercise data recorded by radionuclide angiography for evaluation of the hemodynamic effects of antiarrhythmic drugs, particularly in patients with depressed LV function at rest, have been emphasized by a number of investigators. 12-14 Although an increase of ≥5% absolute EF over a normal resting value has been termed a normal response to symptom-limited exercise, 15 no change or a decrease in EF during exercise has been noted in some patients with cardiomyopathy¹⁶ and with coronary artery disease. 12 Our 29 patients responded to exercise before mexiletine treatment with a median increase of 5%. The median response to exercise was reduced after 1 and 3 months of mexiletine treatment in the group with a baseline EF >40% but showed a small increase over baseline at both study intervals in the group who had a baseline EF ≤40%.

In a recently published retrospective study¹⁷ of 6 antiarrhythmic drugs, mexiletine was found to be associated with the second lowest incidence, after lorcainide,

of newly induced or worsened existing congestive heart failure (0.9 and 2.0%, respectively). In our study, which included 5 patients with a baseline EF below 35%, none of the patients developed symptoms or signs of congestive heart failure during mexiletine therapy.

Results comparable to ours were obtained by Rutledge et al,8 who used daily mexiletine doses up to 1,200 mg in patients with a mean baseline LVEF of 32% during an average treatment period of 14 months, and by Sami and Lisbona⁹ in patients with coronary artery disease and congestive heart failure, most of whom required daily doses of 600 to 900 mg for control of ventricular tachycardia. In neither of these studies were any significant changes in LVEF seen during mexiletine therapy.

The average arrhythmia suppression rates obtained with mexiletine measured up to the efficacy criteria applied but showed a slight decline at the end of 3 months of treatment, during which no dose adjustments were allowed.

We also determined whether any relation exists between the effect of mexiletine on LVEF and its success in suppressing ventricular arrhythmias. Not unexpectedly, group 2 patients (i.e., those with more severe ventricular dysfunction) had a higher mean hourly VPC frequency at baseline than group 1 and, perhaps because of this, responded to mexiletine with a greater average reduction than did group 1. However, the scatter plots of our individual patients' changes in VPC rate and EF over the course of the study show no correlation between the magnitude of the treatment effect on LV function and the degree of arrhythmia suppression. This finding is at variance with the observations of Meissner et al. 18 These investigators assessed the suppression of inducible ventricular tachycardia or ventricular fibrillation in the electrophysiologic laboratory, whereas we assessed the suppression of spontaneous VPCs and spontaneous ventricular tachycardia by ambulatory Holter electrocardiography.

Our results, including the observed absence of any significant changes in blood pressure, heart rate or electrocardiographic intervals and the lack of any symptoms of congestive heart failure after mexiletine treatment, substantiate previously published clinical data suggesting that long-term use of oral mexiletine is efficacious and relatively free of cardiac depressant effects, even in patients with diminished LV function. We found no evidence of any correlation between treatment-induced changes in LVEF and the suppression of arrhythmias.

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Effectiveness of the Once-Daily Calcium Antagonist, Lacidipine, in Controlling 24-Hour Ambulatory Blood Pressure

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The efficacy of the new once-daily dihydropyridine calcium antagonist, lacidipine, in reducing ambulatory intraarterial blood pressure (BP) was examined in 12 untreated hypertensive patients. The intraarterial recording was commenced 24 hours before the first 4-mg dose and was continued for a further 24 hours thereafter. After dose titration and chronic therapy, a second 24-hour ambulatory BP recording was made. There was a steady onset of drug action, maximal at 2 hours, but with a reflex tachycardia after the first dose. Chronic administration reduced BP throughout the 24-hour period, without tachycardia. Mean daytime reduction in BP was 20 mm Hg systolic (p < 0.005) and 12 mm Hg diastolic (p <0.02). Mean nighttime reduction was 8-mm Hg systolic (p <0.05) and 6mm Hg diastolic (difference not significant). There was no postural decrease in BP on 60° head-up tilting and hypotensive action was maintained during isometric exercise (reduction at peak of 32/18 mm Hg, p <0.05) and throughout dynamic exercise (reduction at peak of 23/14 mm Hg, p <0.05). Lacidipine is an effective once-daily antihypertensive agent, with good control of stress response.

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acidipine is a new dihydropyridine calcium antagonist that has been shown to have typical pharmacologic activity but with a longer duration of action and greater potency on a weight-for-weight basis. It has a selective peripheral vasodilatory action that results in a reduction in peripheral vascular resistance, a compensatory increase in heart rate and an increase in stroke volume. In healthy volunteers a significant reduction in blood pressure (BP) has been detected 24 hours after dosing on a once-daily dosage regimen. Dose titration studies in patients with mild to moderate hypertension have demonstrated a dose-related antihypertensive activity over the range of 2 to 6 mg (data on company file, Glaxo Group Research, Ltd., Greenford, Middlesex, United Kingdom). This study determines the profile of BP reduction by lacidipine over 24 hours after a single daily dose in ambulatory hypertensive patients. The efficacy of the drug in controlling BP during isometric and dynamic exercise, and its effects on postural BP control were also assessed.

METHODS

Patients: Patients were recruited from the Harrow Hypertension Clinic. They were considered for inclusion in the study if their clinical diastolic BP, measured sphygmomanometrically, was ≥95 mm Hg after 3 consecutive visits at least 1 week apart, during which period they had not been receiving any medication. Both men and women between the ages of 21 and 75 years were screened for inclusion, but women of child-bearing potential were excluded, as were those with secondary or malignant hypertension, other cardiac disease, or any other clinically important pathologic condition.

All patients gave written informed consent, and the study was approved by the Harrow Health Authority ethics committee.

Study design: This was an open study, with dose titration from 4 to 8 mg. It has been shown that there is no placebo effect on intraarterial BP measurements and we considered a placebo arm to be unethical in an invasive BP monitoring study.

At entry, BP was measured using a mercury-in-glass sphygmomanometer. If the entry criteria were satisfied, intraarterial ambulatory recording was begun. The next day, after 24 hours of monitoring, patients underwent a program of physiologic testing before receiving their first dose of lacidipine 4 mg. Monitoring was continued for a further 24 hours, after which the intraarterial can-

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nula was removed. Patients continued to take lacidipine 4 mg once daily at 10 AM for 2 weeks.

At the 2-week visit, 3 cuff BP measurements were recorded. If BP control was satisfactory (average diastolic BP ≥90 mm Hg, or a decrease in average diastolic BP of ≥15 mm Hg) patients continued on the same dose for at least another 2 weeks, and then underwent a second period of intraarterial BP monitoring, commencing immediately after the morning dose. Physiologic testing was performed at the end of the 24-hour period. before removal of the cannula. Patients whose diastolic BP was not controlled were given 6 mg of lacidipine for another 2-week period, and, if still not controlled, the dose was then increased to 8 mg/day. BP was checked by cuff at 2-week intervals and arrangements made for the second period of monitoring when it had been satisfactorily controlled on a stable dose for 4 weeks. Blood and urine samples were taken for routine hematologic and biochemical screening at entry, after 4 weeks and at completion of the study.

Intraarterial ambulatory blood pressure recording: The technique of ambulatory BP monitoring used in this laboratory has been previously fully documented.2 A disposable 3Fr gauge cannula was introduced into the brachial artery of the nondominant arm under local anesthesia, using a sterile Seldinger technique. This was connected through a 1-m length of tubing to a specially designed transducer-perfusion unit, which infused heparinized saline in a concentration of 10 IU/ml at a rate of 1.5 × ml/hour. The BP signal from the transducer and the electrocardiogram from bipolar chest leads were recorded on a miniature tape recorder (Oxford Medilog MK 1), which also incorporated a time channel with an event marker. BP frequency response was flat from 0 to 8 Hz. The equipment is designed so that patients may be fully ambulant and carry out their normal daily activities.

Physiologic testing: After 24 hours of ambulatory recording, the patients underwent a standardized series of physiologic tests, beginning with 20 minutes of supine rest, followed by 60° head-up tilt maintained for 2 minutes. Isometric exercise was then performed, using 50% of maximum voluntary contraction on a handgrip dynamometer, maintained for 2 minutes. After ≥5 minutes rest, patients commenced maximal dynamic exercise using bicycle ergometry, beginning at a work load of 50 W and increasing by 50-W increments. Each work load was maintained for 5 minutes unless stopped at the patient's request.

Analysis of data: The ambulatory tape recordings were replayed and written out on a linear direct-writing recorder (Watanabe) to allow assessment of analog signal quality and elimination of any artifact.³ Hourly sections were analyzed on a dedicated computer to give mean levels of systolic and diastolic BP and heart rate. Hourly mean values for all the patients were pooled, and curves were constructed to show the 24-hour profiles of BP and heart rate before treatment, after the first dose, and at the completion of lacidipine therapy. Mean daytime and nighttime pressures were calculated and the differences between untreated, first dose and

chronic dose values were compared using Student's paired t test (2-tailed). Because there was a slight variation in the exact time of administration of the first dose, the BP for the 6 hours from the time of dosing in each patient was calculated and compared with the same 6 hours from the previous day.

BP and heart rate during the last 5 minutes of supine rest, and during tilt, isometric and dynamic exercise were computed using a standard digitizing program, which has been described previously. Results before and after treatment with lacidipine were compared using Student's paired t test (2-tailed). Mean values of sphygmomanometric measurements of BP at entry into the study and on the final day of treatment were pooled and compared, again using Student's paired t test (2-tailed). A p value <0.05 was considered significant.

RESULTS

Clinical course: Twelve patients (4 men, 8 women), mean age 54 years (range 41 to 70), were entered into the study. One patient had a very severe headache after the first dose (4 mg) of lacidipine and refused to continue. The data from this patient were included in the analysis of the first dose response, but were excluded thereafter. The other 11 patients completed the study. One patient failed to take her first dose of lacidipine until 4 PM, and her data were excluded from analysis for the 24-hour profile after the first dose. She was, however, included in all other analyses. Hypertension in 2 patients was controlled with 4 mg of lacidipine; 7 patients were titrated to 6 mg and 2 to 8 mg.

Seven patients complained of headache, flushing or fullness in the head during the course of therapy. In 2 patients this was after the first dose, 1 of whom subsequently withdrew. In 5, it occurred later and persisted, but was not severe enough to cause the patients to withdraw from the study. Three patients developed severe ankle edema when taking a dose of 6 mg. All these patients completed the study, but in 1 an indicated dose increment to 8 mg was withheld. No patient developed

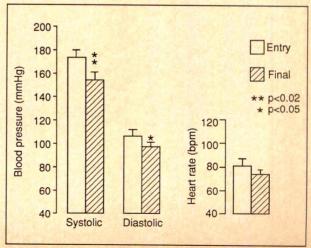


FIGURE 1. Mean heart rate and blood pressure measured sphygmomanometrically before and after chronic dosing with lacidipine. *Bars* represent standard error.

TABLE I Intraarterial Blood Pressure and Heart Rate During Physiologic Tests

Supine rest (last 5 of 20 min) 9 Systolic BP (mm Hg) Diastolic BP (mm Hg) Heart rate (beats/min ⁻¹)	161 90 83	136 78 84	<0.05 NS
Systolic BP (mm Hg) Diastolic BP (mm Hg) Heart rate (beats/min ⁻¹)	90	78	
Diastolic BP (mm Hg) Heart rate (beats/min ⁻¹)			NC
	83	9/	140
		04	NS
Head-up tilt			
15 seconds 9			
Systolic BP (mm Hg)	170	136	< 0.02
Diastolic BP (mm Hg)	99	81	< 0.005
Heart rate (beats/min ⁻¹)	90	89	NS
30 seconds 9			
Systolic BP (mm Hg)	170	138	< 0.05
Diastolic BP (mm Hg)	102	82	< 0.05
Heart rate (beats/min ⁻¹)	87	89	NS
60 seconds 9			
Systolic BP (mm Hg)	169	144	NS
Diastolic BP (mm Hg)	104	86	< 0.05
Heart rate (beats/min ⁻¹)	90	91	NS
90 seconds 9			
Systolic BP (mm Hg)	172	144	<0.05
Diastolic BP (mm Hg)	104	86	<0.05
Heart rate (beats/min ⁻¹)	90	92	NS

any significant hematologic or biochemical derangement during the course of the study.

Pooled systolic and diastolic BP measurements for 11 patients at entry and completion of the study are shown in Figure 1. Both systolic and diastolic BPs were significantly reduced, and no change in heart rate was noted.

Intraarterial ambulatory blood pressure: Technically adequate BP recordings were obtained in all patients.

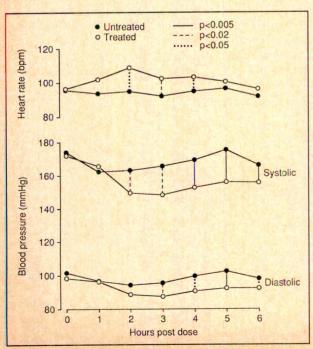


FIGURE 2. Blood pressure and heart rate during the 6 hours after the first dose of lacidipine, compared with the same 6 hours the previous day.

BP and heart rate response to the first dose of lacidipine is shown in Figure 2. BP decreased steadily from dosing and a significant reduction was demonstrated 2 hours after dosing.

The 24-hour profiles plotted from consecutive mean hourly BPs and heart rates in 11 patients, untreated and after their first 4-mg dose of lacidipine, are shown in Figure 3A, and similar profiles for 11 patients, untreated and after 4 weeks of therapy at their maximal titrated dose, are shown in Figure 3B. A significant reduction in daytime pressure was observed after the first dose, but the curves coincided by 8 PM. A similar coincidence was seen after full dose titration, but in this case the curves then divided again and a significant reduction in both systolic and diastolic BP was observed at 9 AM, 23 hours after the last dose of the drug. After full dose titration, there was a reduction in mean daytime BP of 20/12 mm Hg (p < 0.05 systolic, p < 0.02 diastolic) and a reduction in mean nighttime pressure of 8/6 mm Hg (p <0.05 systolic, difference not significant for diastolic). No significant change in heart rate was demonstrated.

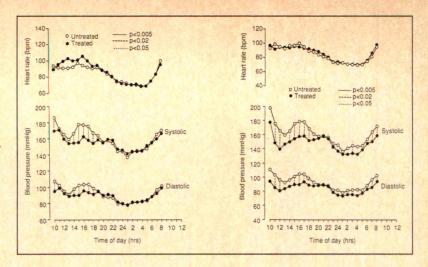
BP and heart rates during rest and for 90 seconds of 60° head-up tilt are listed in Table I. BP at peak of isometric handgrip in untreated patients and approximately 22 hours after the last titrated dose of the drug is shown in Figure 4. BP was significantly reduced by therapy in all these physiologic tests, but no significant postural drop occurred on tilting. BP and heart rates during bicycle dynamic exercise before and at completion of therapy are shown in Figure 5. BP was significantly reduced (p <0.05) during bicycle exercise up to the fifth minute, when 9 patients were still exercising. The trend was continued throughout exercise, but insufficient numbers of patients exercised longer than 5 minutes for the differences to be meaningful. There was no difference in the percent increase in BP from rest to peak exercise between treatment assessment before and after treatment during either isometric or dynamic exercise.

DISCUSSION

The effect of calcium antagonist drugs in reducing BP is mediated by a reduction in vascular smooth muscle tone, thereby reducing the raised peripheral vascular resistance, which is the consistent hemodynamic abnormality in essential hypertension. This vasodilation may, however, result in a reflex tachycardia, orthostatic hypotension, flushing and headache. These adverse effects may be reduced by the use of long-acting or slow-release preparations, which achieve a smooth plasma level without sudden peaks. Moreover, it has been suggested that compliance is improved by once-daily therapies, specially in asymptomatic conditions such as hypertension. Thus, a calcium antagonist with an effective 24-hour duration of action should be useful in the treatment of this condition.

Our results show that BP decreased gradually after the first dose of lacidipine, with no acute decrease in pressure, and, after optimal dose titration to suit individual patient requirements, lacidipine effected a

FIGURE 3. Twenty-four hour blood pressure curves in 11 patients. Left panel, untreated and after their first 4 mg dose of lacidipine; right panel, untreated and after full-dose titration (4 to 8 weeks treatment).



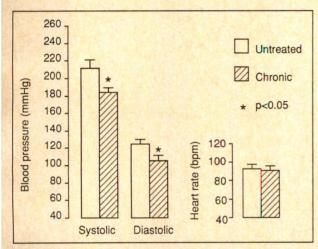


FIGURE 4. Mean blood pressure and heart rate at peak of isometric exercise. Bars represent standard error.

smooth reduction in BP throughout 24 hours, with a mean daytime reduction of the same order as other calcium antagonists. 9,12,13 Although a reflex tachycardia occurred after the first dose of the drug, heart rate at the end of the treatment period was similar to the rate at baseline, suggesting a "resetting" of the baroreceptor reflex. This is consistent with the suggestion outlined above—that vasodilatory side effects may be reduced once a steady plasma level is achieved. Firm conclusions about the incidence of headache and ankle-swelling that persisted at the end of the treatment period cannot be made, as only a small number of patients were studied.

We believe it is prognostically important to reduce BP throughout 24 hours, both at rest and during stress, although data to confirm this are not available. Other investigators have suggested that basal BP,14 early morning increase in BP15 and the BP response to normal daily stress16 are more closely associated with cardiovascular events than is the casual daytime BP. Nevertheless, it is by casual clinical BPs, measured sphygmomanometrically, that BP control must of necessity be assessed. Thus, we measured mean daytime and mean nighttime intraarterial pressures, and the BP response to isometric and dynamic exercise and also cuff BPs at

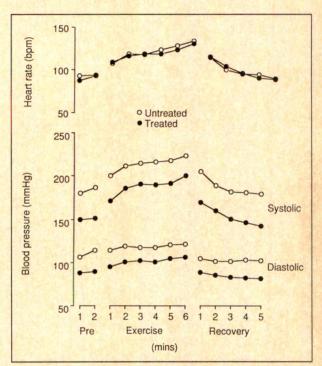


FIGURE 5. Mean blood pressure and heart rate during bicycle exercise. Bars represent standard error.

entry and completion of the study. Like other calcium antagonists, lacidipine did not affect diurnal variation, or the proportional increase in BP during exercise, as would be expected with a drug that does not alter autonomic tone. Nevertheless, 24-hour BP reduction is achieved with this drug.

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Atendol Therapy for Exercise-Induced Hypertension After Aortic Coarctation Repair

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After successful repair of coarctation of the aorta in childhood, exercise-induced upper body systolic hypertension is well documented. Beta blockade has been shown to reduce the arm/leg gradient in untreated coarctation of the aorta; treatment before coarctation repair has decreased paradoxical hypertension after repair. Ten patients with successful surgical repair of coarctation, defined as a resting arm/leg gradient of ≤18 mm Hg, were evaluated by treadmill exercise before and after β blockade with atenolol. Mean age was 5.5 years at repair and 18 at study. At baseline evaluation, systolic blood pressures at termination of exercise ranged from 201 to 270 mm Hg (mean 229 mm Hg). Arm/leg gradients at exercise termination ranged from 30 to 143 mm Hg (mean 84). Followup treadmill exercise studies were performed after β blockade. Upper extremity systolic pressures at exercise termination were normalized in 9 of 10 patients. Maximal systolic blood pressure recorded at exercise termination ranged from 163 to 223 mm Hg (mean 196 mm Hg, p ≤0.005). Arm/leg gradient at termination of exercise also decreased significantly to a mean of 51 mm Hg (p ≤0.05). No patient had symptoms on atenolol and exercise endurance times were unchanged.

The study results in this small series suggest that cardioselective β blockade can be used to treat exercise-induced upper body hypertension effectively after surgical repair of coarctation. Because a high incidence of premature cardiovascular disease has been well documented after satisfactory surgical repair, the findings are of importance for this group of postoperative patients.

(Am J Cardiol 1990;66:1233-1236)

n exaggerated upper body hypertensive response to exercise after repair of coarctation of the aorta has been well described. 1-5 Such hypertension theoretically leaves patients at an accelerated risk for acquired cardiovascular disease despite satisfactory surgical repair with elimination of resting upper extremity hypertension and arm/leg pressure gradients. Longterm follow-up studies have documented significant cardiovascular morbidity and premature mortality in patients who have undergone satisfactory surgical repair of coarctation.⁶⁻⁹ Persistent systolic hypertension in the context of increased cardiac output, such as with exercise, would be anticipated to contribute to this. Pharmacologic treatment with β blockade has been shown to reduce upper limb hypertension and arm/leg gradient before coarctation repair. 10 Treatment with β blockade before coarctation repair has resulted in a significant decrease in acute paradoxical hypertension postoperatively.11 This study was undertaken to evaluate the effect of cardioselective β blockade on exercise-induced upper extremity hypertension and arm/leg gradient after coarctation repair.

METHODS

The records of the Division of Pediatric Cardiology were reviewed for patients >10 years of age who had undergone previous repair of isolated coarctation of the aorta. To exclude residual coarctation of the aorta as the cause of hypertension, only patients with resting arm/leg systolic blood pressure difference ≤18 mm Hg were considered for inclusion. Those who had undergone previous treadmill testing with exercise-induced upper extremity systolic blood pressure ≥220 mm Hg, or arm/leg gradient ≥30 mm Hg, or both, were contacted; of these, 13 agreed to undergo evaluation.

Treadmill exercise: Initial blood pressure measurements were taken in the supine position. Right arm blood pressure was determined with an oscillometric device (Dinamapp Model 1846SX) using a cuff of appropriate size. Blood pressures taken in this way have been shown to correlate well with direct central aortic and radial artery pressures. 12,13 Right leg systolic blood pressure was determined using a standard leg cuff on the thigh with a Doppler probe over the popliteal artery. Heart rate and rhythm were monitored continuously using leads V₁, V₅ and aVF. Patients were exercised using the modified Bruce protocol. Right arm and leg blood pressures were recorded immediately after termination of exercise, as were heart rate and electrocardiogram. These determinations were repeated every 2 minutes throughout the 10-minute recovery period.

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TABLE I Characteristics of Study Group Atenolol BP Exercise BP Baseline BP Surgical Age at Years of A/L Grad A/L Grad A/L Grad Follow-Up Technique Pts Repair (vr) 249/69, 109 209/63.79 126/76,14 R/E 11 9 1 185/70.28 260/80, 122 120/70.3 9 R/E 2 7 191/61,39 210/80,30 PA 132/70.0 1 17 3 214/72,18 136/60, 18 270/65,69 SFA 3 4 14 220/60,91 163/65,51 118/50.0 19 R/E 5 1/12 203/76,60 220/70.143 144/80.9 20 R/E 1/12 6 140/78.15 240/60,73 196/61,66 R/E 5 7 12

A/L Grad = systolic blood pressure difference in mm Hg between right arm and either leg; BP = blood pressure; PA = patch angioplasty; R/E = resection and end-to-end anastomosis; SFA = subclavian flap angioplasty.

PA

R/E

R/E

126/82,0

147/77.0

126/62,0

Of the 13 potential patients, 10 demonstrated upper extremity systolic blood pressure \geq 220 mm Hg, or arm/leg gradient \geq 30 mm Hg, or both, with treadmill evaluation. Each patient was begun on atenolol 50 mg once in the morning. Patients were reevaluated within 4 weeks. Resting and exercise heart rates were not decreased by 25% in 6 patients, so the dose of atenolol was increased until effective β blockade was achieved. Treadmill blood pressure results on this final dosage are those reported. Of the 10 patients, 4 were receiving atenolol 50 mg, 1 was receiving 75 mg and 5 were receiving 100 mg at the time of this report.

7

9

7/12

4

11

19

RESULTS

8

10

Study results are listed in Table I. On pretesting evaluation (before exercise testing), systolic blood pressures ranged from 106 to 140 mm Hg (mean 128). While all pressures were within the normal range, the systolic blood pressure was above the 80th percentile in 8 of 10 patients when compared with age- and genderspecific normal subjects. ¹⁴ Diastolic blood pressures were normal in all subjects. Resting arm/leg gradients were only present in 5 patients and ranged from 3 to 18 mm Hg (mean 7).

At baseline treadmill evaluation, resting systolic blood pressures in the upper extremity were higher, ranging from 117 to 153 mm Hg; systolic blood pressures in 9 of 10 patients were above the 95th percentile compared with age- and gender-specific normal subjects. Diastolic blood pressures were unchanged. Arm/ leg gradients were present in 8 patients, ranging from 7 to 36 mm Hg (mean 13). The increase in systolic blood pressure and in arm/leg gradient before treadmill testing was attributed to anticipatory anxiety. Peak exercise heart rates reached the predicted maximum in all patients, ranging from 186 to 202 per minute. Upper extremity systolic blood pressures at exercise termination ranged from 201 to 270 mm Hg (mean 229). Arm/leg gradients increased in all patients with a range of 30 to 143 mm Hg and a mean of 84.

After β blockade with atenolol, resting heart rates significantly decreased to a mean of 62 per minute (range 47 to 75 p \leq 0.005). Resting upper extremity blood pressures also significantly decreased to 115 to 143 mm Hg (mean 129). Although this did not reach

statistical significance, systolic blood pressures did fall into the normal range in 7 of 10 patients. Arm/leg gradients persisted at rest with atenolol in 7 patients, ranging from 7 to 19 mm Hg. With atenolol, peak exercise heart rates were significantly reduced to a mean of 154 per minute (p ≤0.005). Upper extremity systolic blood pressures at exercise termination normalized in 9 of 10 patients, as shown in Figure 1. The maximal systolic blood pressure recorded at peak exercise ranged from 163 to 223 mm Hg (mean 196), a significant decrease compared with baseline reading (p ≤0.005). Exercise arm/leg gradients also significantly decreased to a mean of 51 mm Hg (p ≤ 0.05). In 1 patient, effective β blockade did not decrease systolic hypertension with exercise and treatment was discontinued. No patient had symptoms related to atendol therapy. Endurance times after β blockade did not differ significantly from times before treatment (Figure 2).

201/68,63

216/84,74

207/67,65

165/57,30

203/60.33

223/68, 109

DISCUSSION

In this group of patients, studied after satisfactory surgical repair of coarctation of the aorta, severe exercise-induced upper extremity systolic hypertension was effectively treated by cardioselective β blockade. Blood pressure response to exercise normalized, and arm/leg gradients were reduced. Patients had no symptoms related to atenolol either during the study or on follow-up (now of 24 months), and treadmill endurance times were unchanged. Cardioselective β blockade would appear to be a safe and effective way to treat exercise-induced upper limb hypertension in this context.

Many mechanisms have been proposed as the etiology of this hypertensive response. Beekman et al¹⁵ demonstrated altered baroreceptor function in patients who remain hypertensive after satisfactory coarctation repair; this mechanism may contribute to the hypertensive response to exercise even when resting blood pressures are normal. Histologically, the aortic wall before coarctation has been shown to be more rigid than the wall below coarctation and this difference may well persist after surgical repair. Increased vascular resistance and abnormal reactivity in the upper extremities, with normal resistance and reactivity in the lower extremities, has been demonstrated long after coarctation repair ^{17,18}; this could certainly contribute to the hypertensive re-

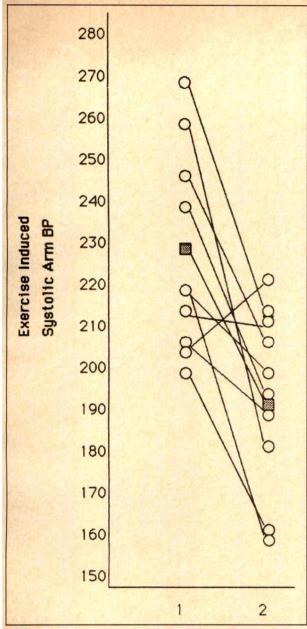


FIGURE 1. Systolic blood pressure (BP) at exercise termination in the 10 study patients before (1) and after (2) β blockade with atenolol.

sponse to exercise. A minimal residual anatomic narrowing may result in no significant systolic gradient at rest as well; however, with the increased cardiac output with exercise, the same mild degree of narrowing can result in a significant gradient and in upper extremity hypertension.^{3,19} It seems likely that some combination of these mechanisms represents the etiology of exerciseinduced upper extremity hypertension after satisfactory surgical repair of coarctation.

Beta blockade is known to produce a powerful suppression of the cardiac chronotropic response to exercise. Concurrently, systolic blood pressure is reduced at rest and at all levels of exercise. Cumming and Mir, 10 in a catheterization study of patients with coarctation, used propranolol to demonstrate that the decrease in

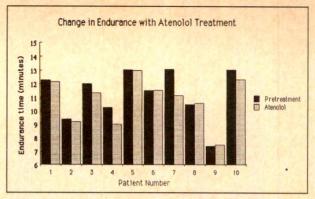


FIGURE 2. Treadmill exercise endurance times in the 10 study patients before and after β blockade with atenolol.

blood pressure after β blockade is due to a decrease in cardiac output mediated almost entirely by the decrease in heart rate, with little if any decrease in stroke volume. Cardioselective β blockade with atenolol has been shown to produce the same hemodynamic response as nonselective β blockade with propranolol.²⁰ Potentially important humoral and metabolic effects of nonselective β blockade are avoided by using atenolol.

Late follow-up studies after coarctation repair demonstrate important residual problems. In particular, a high incidence of premature cardiovascular disease has been well documented, with a significant risk for early mortality even with apparently satisfactory surgical repair. 6-9 The duration of preoperative hypertension has been identified as a significant risk factor for persistent hypertension and early cardiovascular disease. 6,9 However, even in patients who have undergone surgery at an early age with a satisfactory resting result, severe upper extremity hypertension with exercise is common. Exercise is used as an analogue for the wide variety of physiologic stresses resulting in increased cardiac output that occur in everyday life. Systolic hypertension is known to be a powerful predictor of cardiovascular morbidity in adults. 21,22 There would therefore appear to be a good rationale for treatment of an exaggerated systolic hypertensive response to exercise in patients after coarctation repair, most of whom had considerable systolic hypertension of variable duration before their operations. The results in this small series suggest that cardioselective β blockage can be used to achieve this result safely and effectively.

Acknowledgment: We gratefully acknowledge the secretarial assistance of Terry Howe and Cindy Shear-

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Risk of Cardiovascular Mortality in Alcohol **Drinkers, Ex-Drinkers and Nondrinkers**

Arthur L. Klatsky, MD, Mary Anne Armstrong, MA, and Gary D. Friedman, MD

Lower cardiovascular mortality rates in lighter drinkers (versus abstainers or heavier drinkers) in population studies have been substantially due to lower coronary artery disease (CAD) mortality. Controversy about this U-shaped curve focuses on whether alcohol protects against CAD or, because of other traits, whether abstainers are at increased risk. Inclusion of ex-drinkers among abstainers in some studies has led to speculation that this might be the trait increasing the risk of abstainers. This new prospective study among 123,840 persons with 1,002 cardiovascular (600 CAD) deaths showed that ex-drinkers had higher cardiovascular and CAD mortality risks than lifelong abstainers in unadjusted analyses, but not in analyses adjusted for age, gender, race, body mass index, marital status and education. Use of alcohol was associated with higher risk of mortality from hypertension, hemorrhagic stroke and cardiomyopathy, but with lower risk from CAD, occlusive stroke and nonspecific cardiovascular syndromes. Subsets free of baseline cardiovascular or CAD risk had Ushaped alcohol-CAD curves similar to subsets with baseline risk. Among ex-drinkers, maximal past intake and reasons for quitting (medical versus nonmedical) were unrelated to cardiovascular or CAD mortality. These data show that: (1) alcohol has disparate relations to cardiovascular conditions; (2) higher cardiovascular mortality rates among exdrinkers are due to confounding traits related to past alcohol use; and (3) the U-shaped alcohol-CAD relation is not due to selective abstinence by persons at higher risk. The findings indirectly support a protective effect of lighter drinking against CAD. (Am J Cardiol 1990;66:1237-1242)

isparities in the relations of cardiovascular disorders to the use of alcoholic beverages have become apparent. Heavier drinking is related to higher prevalence of cardiomyopathy, 1-3 hypertension,4 hemorrhagic stroke5-7 and cardiac dysrhythmias.8,9 Lighter drinking, in many population studies cited in recent reports, 6,10,11 is related to lower prevalence of both coronary artery disease (CAD) and, in a few studies, 6,7 occlusive cerebrovascular disease. In several other studies of cardiovascular mortality, 12-15 abstainers are at highest risk, with both lighter and heavier drinkers at lower risk. The composite of these disparate relations in several population studies of cardiovascular mortality has been a U-shaped curve (lighter drinkers at lower risk than abstainers or heavier drinkers). CAD deaths comprise the majority of these cardiovascular deaths.

The possibility that lighter alcohol use protects against CAD is supported by plausible hypothetical mechanisms. These include a favorable effect on highdensity lipoprotein cholesterol (HDL) concentration¹⁶⁻¹⁸ and apolipoproteins, ^{18,19} and a possible antithrombotic effect. 6,7,10 Controversy about protection persists, however, on the grounds that correlates of abstinence and lighter drinking could explain the higher risk of abstainers. A widely publicized^{11,20} hypothesis was that many abstainers are former drinkers who abstain because of symptoms, CAD diagnosis, or other traits that predispose to CAD events, thus spuriously producing an apparent lower CAD risk among drinkers. Several of the reported population studies did include ex-drinkers among abstainers.

Herein are reported findings from a new large prospective study of mortality, in which lifelong abstainers are separated from ex-drinkers. Attention is given to reasons for stopping or decreasing alcohol intake and to evidence of prior cardiovascular or CAD risk.

METHODS

We studied 129,170 persons who underwent health examinations in a prepaid health plan from January 1978 through December 1985. The procedure included a questionnaire about current and past medical history, a panel of health screening tests and laboratory tests. For persons who had >1 examination, we used data from the first.

Based on a special alcohol questionnaire, we defined as lifelong abstainers nonusers who answered that they never or almost never drank alcohol in the past. Exdrinkers were nondrinkers in the past year who indicated that they had taken alcohol previously. Ex-drinkers

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TABLE I Alcohol Use and Crude Death Rates in Study Population CV Deaths Non-CV Deaths Rate/1,000 Rate / 1.000 Mean Age No Person-Years No. Person-Years **Drinking Category** 194 25 202 2.6 15 030 436 Nondrinkers 94 47 76 3.8 3.998 46.4 **Ex-drinkers** 44.9 28 3.6 27 3.4 1 542 <1/day 12 40 588 47 4 16 54 1 to 2/day 26 3.7 1.452 47.1 36 5.1 ≥3/day Drinkers 26,479 40.5 287 2.1 220 1.6 <1/month 46 299 37.8 364 1.5 247 1.0 <1/day,>1/month 158 25 14 22.548 42.3 292 1 to 2/day 8.168 42.5 143 3.4 72 1.7 3 to 5/day 27 2.8 5.6 54 ≥6/day 1.910 41.6 Reason reduced intake 125 14.537 41.5 237 3.2 1.7 Medical 201 13 Nonmedical 30,986 39.0 308 20 2.1 308 2.0 7,282 42.4 80 Weight loss Ex-drinkers Reason quit 45 5.5 33 4.1 1.645 48.0 Medical 43 3.6 Nonmedical 2.353 454 49 41 1,428 2.2 1.002 1.6 124,432 40.5 Total CV = cardiovascular

	All Causes	(n = 2,430)	Non-CV (n	= 1,428)	CV (n = 1,002)		
Drinking Category	RR	95% CI	RR	95% CI	RR	95% CI	
Abstainers	1.0	(reference)	1.0	(reference)	1.0	(reference)	
Ex-drinkers	1.1	0.9-1.4	1.3 [†]	1.0-1.7	1.0	0.8-1.3	
<1/day [‡]	1.2	0.9-1.6	1.2	0.8-1.8	1.2	0.8-1.8	
1 to 2/day [‡]	1.1	0.7-1.6	1.3	0.8-2.1	0.9	0.5-1.7	
≥3/day [‡]	1.1	0.8-1.5	1.3	0.9-1.9	0.9	0.6-1.4	
Drinkers							
<1/month	1.0	0.9-1.2	1.1	0.9-1.3	0.9	0.8-1.2	
<1/day;>1/month	0.9†	0.8-1.0	0.9	0.8-1.1	0.8†	0.7-1.0	
1 to 2/day	0.9	0.8-1.1	1.1	0.9-1.4	0.79	0.6-0.9	
3 to 5/day	1.0	0.8-1.2	1.3	1.0-1.6	0.8	0.6-1.0	
≥6/day	1.4	1.1-1.8	1.9	1.4-7.6	1.0	0.7-1.5	

* Computed from coefficients estimated by Cox proportional hazards model controlled for age, gender, race, smoking, body mass index, marital status and education.
†p <0.05; †computed from separate model; †p <0.01; |p <0.001.
Cl = confidence interval; CV = cardiovascular; RR = relative risk.

were asked about their reasons for stopping and the largest number of drinks taken regularly for ≥1 year. Drinkers were asked how many drinks they usually had during the past year: ≥9/day, 6 to 8/day, 3 to 5/day, 1 to 2/day, <1/day but >1/month and <1/month (special occasions only). Drinkers also indicated the number of days per week they consumed wine, beer and hard liquor. Drinkers who had reduced intake were asked to specify reasons. Reasons for stopping drinking or reducing intake were classified as medical and nonmedical.

All subjects were followed until the earlier of either date of death or December 1985, yielding 655,305 person-years of follow-up. Death was ascertained using an automated matching system,21 and was validated by 2 persons independently. This process uncovered 2,514 deaths or 3.84/1,000 person-years of follow-up. Those (n = 84; 3.3% of deaths) with incomplete alcohol and

tobacco data were eliminated, leaving 2,430 deaths (all causes) for analysis. Primary death certificate diagnoses, converted to International Classification of Diseases, Adapted, Eighth Revision codes, were used. Subsets studied included: all cardiovascular (codes 390 to 459), hypertensive disease (codes 401 to 404), all CAD (codes 410 to 414), acute myocardial infarction (code 410), other CAD (codes 411 to 414), cardiomyopathy (code 425), miscellaneous cardiovascular syndromes (codes 427 to 429), hemorrhagic cerebrovascular (codes 430 to 431), occlusive cerebrovascular (codes 432 to 435), nonspecific cerebrovascular (codes 436 to 438), arterial conditions (codes 440 to 445), all noncardiovascular (except for codes 390 to 459) and cirrhosis (code 571).

We attempted to identify persons who were free of risk that might influence alcohol consumption. A person

TABLE III Relative Risks of Death* from Various Cardiovascular Conditions and Cirrhosis According to Alcohol Use

Condition [†] (no. of deaths)	RR for Each Drinking Category Versus Lifelong Abstainers						
	Ex- Drinkers	<1/mo.	<1/day,>1/mo.	1 to 2/day	3 to 5/day	≥6/day	
All CAD (600)	1.0	0.9	0.8	0.7‡	0.6§	0.8	
AMI (284)	1.0	0.7	0.8	0.6§	0.5§	0.6	
Other CAD (316)	0.9	1.0	0.7	0.8	0.7	1.0	
Cerebrovascular (138)	1.0	0.8	0.8	0.8	0.7	1.4	
Hemorrhagic (41)	1.4	1.5	1.6	1.8	1.3	4.7	
Occlusive (34)	0.9	0.5	0.5	0.3	0.4	_1	
Nonspecific (63)	1.1	0.7	0.9	1.0	1.0	1.2	
Hypertension (64)	2.8	2.4	1.9	1.3	2.2	2.1	
Cardiomyopathy (24)	3.4	8.5 [‡]	4.0	5.6	2.4	8.0	
Syndromes (82)¶	0.6	0.6	0.5	0.4‡	0.6	1.0	
Arterial (41)**	_1	1.1	1.6	0.4	1.7	1	
Cirrhosis (42)	10.8§	1.4	1.0	4.3	8.1‡	22.0 ^{††}	

^{*} Computed from coefficients estimated by Cox proportional hazards models controlled for age, gender, race, smoking, body mass index, marital status and education.

† See text for International Classification of Diseases, Adapted, 8th Revision codes.

was considered at CAD risk if he or she answered "yes" to any of 12 items suggesting any lifetime history of CAD diagnosis, symptoms or risk factors (hypertension, diabetes, hypercholesterolemia). A person was considered at cardiovascular risk if he or she answered "yes" to any of the 12 CAD risk items or to 5 other items indicating possible lifetime non-CAD cardiovascular problems. In selecting the items indicative of baseline CAD or cardiovascular risk, we attempted to include all available predictors. Persons were considered at nonspecific risk, the only category limited to recent problems, if they indicated that they were taking the examination because of illness, or if there had been any hospitalization or major medical problems in the past year.

Age-adjusted and multivariate analyses used the Cox proportional hazards model. For economy, all analyses used a 10% random sample of the entire study population in addition to all cases. Table I lists some descriptive data.

RESULTS

In analyses adjusted only for age, ex-drinkers and heavier drinkers had a significantly higher risk of cardiovascular mortality than did abstainers; relative risks (95% confidence intervals, p value if <0.01) for the categories were: ex-drinkers = 1.5 (1.1 to 1.9, p = 0.004); <1/month = 1.0 (0.8 to 1.2); <1/day but >1/month =0.9 (0.8 to 1.1); 1 to 2/day = 0.9 (0.7 to 1.1); 3 to 5/day = 1.2 (0.9 to 1.6); $\geq 6/day = 1.8$ (1.2 to 2.6, p = 0.006). In analyses adjusted for all covariates, ex-drinkers had a similar cardiovascular mortality risk as abstainers, and current drinkers had a U-shaped relation with the nadir of the U at 1 to 2 drinks/day (Table II). In age-adjusted analyses, ex-drinkers and persons in all drinking categories from 1 to 2/day and higher had significantly greater noncardiovascular mortality risk than abstainers: ex-drinkers = 1.6 (1.3 to 2.1, p < 0.0001); <1/month = 1.1 (0.9 to 1.3); <1/day but >1/month = 1.0 (0.9 to 1.2); 1 to 2/day = 1.4 (1.1 to 1.6, p < 0.001); 3 to 5/day = 1.8 (1.4 to 2.2, p <0.0001); and $\ge 6/\text{day}$ = 2.9 (2.1 to 3.9, p < 0.0001). When the analyses were adjusted for the other covariates, ex-drinkers and heavier drinkers still had higher noncardiovascular mortality risk than abstainers (Table II). The composite all-cause mortality curve was slightly J-shaped in adjusted analysis, with lighter drinkers at a slightly reduced mortality risk and the heaviest drinkers at highest risk. Among the covariates (data not shown), age, male gender, and smoking were powerful predictors of both cardiovascular and noncardiovascular death. Black race and higher body mass index were weakly predictive of cardiovascular but not of noncardiovascular death.

For the subset of CAD deaths with acute myocardial infarction, the relation to alcohol use was inverse at all drinking levels; for less specific CAD events an almost symmetrical U-shaped curve was present among drinkers (Table III).

Among other cardiovascular conditions, alcohol was associated with a higher risk of death attributed to hypertension, cardiomyopathy and hemorrhagic cerebrovascular disease, but with a lower risk of death attributed to occlusive cerebrovascular disease and miscellaneous syndromes (arrhythmias, congestive failure, and so forth, without specified etiology). Because of small numbers, many of the risks for conditions with <50 deaths must be regarded as unstable. Data showing risk of cirrhosis deaths, which showed the expected relations to drinking, are included in Table III.

Lower risk of CAD mortality among drinkers was present in both men and women, but was more pronounced in women (Table IV). The inverse alcohol-CAD relation was consistent in several age brackets and in subsets of persons with and free of baseline risk. Consistency was less in subsets defined by smoking habits, with reduced risk of mortality greatest among ex-smoking drinkers and unclear among lifelong nonsmokers.

See text for international classification of biseases, Adapted, of in Nevision Codes.

†p <0.05; §p <0.01.

Unable to calculate RR due to insufficient number of cases.

Includes symptomatic heart disease (n = 32), other disorders of heart rhythm (n = 22) and ill-defined heart disease (n = 28).

** Includes arteriosclerosis (n = 15), aneurysms (n = 23), peripheral vascular disease (n = 2), and arterial embolism and thrombosis (n = 1).

 $^{^{\}dagger\dagger}$ p <0.001. AMI = acute myocardial infarction; CAD = coronary artery disease; RR = relative risk

TABLE IV Relative Risk of Death* from Coronary Artery Disease in Various Subsets† According to Alcohol Use

	RR for Each Drinking Category Versus Lifelong Abstainers					
Subset (no. of deaths)	Ex-drinkers	<1/mo.	<1/day,>1/mo.	1 to 2/day	3 to 5/day	≥6/day
Men (420)	1.1	1.0	0.9	0.7	0.8	0.9
Women (180)	0.9	0.7‡	0.4§	0.7	0.2‡	0.6
<50 yrs old (48)	1.3	0.4	0.5	0.4	0.6	0.7
50 to 59 yrs old (108)	0.5	0.5	0.6	0.6	0.6	0.7
≥60 yrs old (444)	0.9	0.8‡	0.5§	0.5§	0.49	0.5
Never smoked (231)	1.8 [‡]	1.2	0.9	1.0	0.5	1.8
Ex-smokers (212)	0.4	0.5	0.5§	0.5§	0.39	0.8
Current smokers (213)	1.1	0.7	0.8	0.6	0.9	0.5
Have CAD risk (472)	1.0	0.9	0.8	0.8	0.5	0.9
No CAD risk (118)	1.0	0.8	0.7	0.6	0.6	0.6
Have CV risk (518)	1.0	0.9	0.8	0.7	0.6 [‡]	1.0
No CV risk (77)	0.8	1.0	0.6	0.6	0.5	0.6
	0.9	1.0	0.9	0.8	0.9	1.3
Have nonspecific risk (223) No nonspecific risk (361)	1.1	0.8	0.7	0.7‡	0.4	0.5

^{*} Computed from coefficients estimated by Cox proportional hazards model controlled for age, gender, race, smoking, body mass index. marital status and education. † Computed from separate models; † p <0.05; § p <0.001; † p <0.01.

Abbreviations as in Tables II and III.

Because this raises the possibility that ex-smoking nondrinkers—the reference group for analyses in ex-smokers-could include a disproportionate number of highrisk persons, we studied ex-smokers by baseline risk. Lower CAD mortality rates were present in ex-smokers with and without baseline CAD, cardiovascular and nonspecific risk at all drinking levels. Relative risks (95% confidence intervals) of CAD death in ex-smokers free of CAD risk (n deaths = 37) were, for example: exdrinkers = 0.3 (0.1 to 1.2); <1/month = 0.4 (0.1 to 1.2); <1/day but >1/month = 0.3 (0.1 to 1.0, p)<0.05); 1 to 2/day = 0.3 (0.1 to 1.1); 3 to 5/day = 0.3 $(0.1 \text{ to } 1.5); \ge 6/\text{day} = 2.6 (0.5 \text{ to } 14.5).$

As expected, drinking and smoking were strongly correlated. The proportions of subjects who were never smokers were 81% of abstainers, 29% of ex-drinkers and 46% of all drinkers (24% of persons reporting ≥3 drinks/day). Ex-smokers comprised 8% of abstainers, 49% of ex-drinkers and 25% of drinkers. Ex-drinkers were thus similar to drinkers (probably to heavy drinkers) with respect to exposure to the risks of smoking. Baseline CAD risk, as previously defined, was similar in ex-drinkers and abstainers; it was present in 42.7% of ex-drinking men and in 38.4% of ex-drinking women versus 39.5% of abstaining men and 41.6% of abstaining women (age-adjusted). The 40% of subjects judged to be at high CAD risk comprised 80% of the CAD deaths. Nonspecific risk was more prevalent among exdrinkers than among abstainers; it was present in 44.6% of ex-drinking men and in 50.2% of ex-drinking women versus 37.1 and 35.9%, respectively, of abstaining men and women (age-adjusted).

Reduction or cessation of drinking for medical reasons was associated with a higher risk of noncardiovascular mortality, but not with a higher risk of cardiovascular or CAD mortality (Table V). Only reduction of intake for purposes of weight loss was associated with a higher risk of CAD mortality. Obesity and attempts to reduce are almost surely correlated with several CAD risk factors. However, specified medical reasons for stopping drinking, given by approximately 17% of exdrinkers, were seldom cardiovascular (<1% of ex-drink-

No major differences were apparent in the relations between usage of specific beverages and mortality (Table VI). Within the scheme of categorization chosen (use of the beverage type ≥2 days/week), some persons are represented in >1 beverage use group.

TABLE V Relative Risk of Death* Among Drinkers and Ex-Drinkers According to Reason for Reduction or Cessation

	Relative Risk			
Reason (no. of deaths)	Non-CV	CV	CAD	
Drinkers†			17.11	
Medical (362)	1.4 [‡]	1.1	1.1	
Weight loss (138)	1.1	1.1	1.49	
Nonmedical (509)	1.1	1.0	1.1	
Ex-drinkers†				
Medical (78)	1.5§	1.1	0.9	
Nonmedical (92)	1.2	1.0	1.0	

 $^{^{\}circ}$ Computed from coefficients estimated by Cox propositional hazards model controlled for age, gender, race, smoking, body mass index, marital status and education; $^{\circ}$ separate regressions (reference for drinkers is those with no reduction; reference for ex-drinkers is lifelong abstainers); $^{\circ}$ p <0.001; $^{\circ}$ p <0.05. Abbreviations as in Tables I and IIII.

TABLE VI Relative Risk of Death According to Use of Wine, Beer and Liquor*

RR (95% CI)				
Wine	Beer	Liquor		
0.8 (0.7–0.9) [†] 1.0 (0.8–1.2) 0.7 (0.5–0.9) [†] 0.5 (0.4–0.7) [§] 5.6 (1.1–27.7) [‡]	0.9 (0.8–1.1) 1.1 (0.9–1.4) 0.8 (0.6–1.0) 0.7 (0.5–0.9) [‡] 5.1 (0.9–28.5)	1.0 (0.8–1.1) 1.2 (1.0–1.5) 0.8 (0.6–1.0) [‡] 0.6 (0.5–0.8) [†] 4.8 (0.9–24.6)		
	Wine 0.8 (0.7-0.9)† 1.0 (0.8-1.2) 0.7 (0.5-0.9)† 0.5 (0.4-0.7)§	Wine Beer 0.8 (0.7-0.9)† 0.9 (0.8-1.1) 1.0 (0.8-1.2) 1.1 (0.9-1.4) 0.7 (0.5-0.9)† 0.8 (0.6-1.0) 0.5 (0.4-0.7)§ 0.7 (0.5-0.9)‡		

^{*} Two or more days/week vs abstainers, with separate models for each beverage type and cause, controlled for age, race, gender, smoking, body mass index, marital status and education; wine drinkers: n = 28,488 (426 deaths); beer drinkers: n = 21,152 (318 deaths); liquor drinkers: n = 20,492 (597 deaths). † p < 0.01; † p < 0.05; † p < 0.001.

Abbreviations as in Tables II and III

DISCUSSION

This study confirms the main relations between alcohol use and mortality that have been found previously. The major findings are a higher risk of noncardiovascular mortality for heavier drinkers and a clear U-shaped relation between amount of alcohol intake and cardiovascular death. Data for overall cardiovascular mortality are dominated by the diagnostic groups inversely related to alcohol use, of which CAD is the most noteworthy. The disparities in relations to alcohol make it wise. when possible, to look at cardiovascular conditions separately. The inverse alcohol-CAD relation was also found for CAD hospitalizations in a portion of this cohort. 10 A lower risk of CAD hospitalizations was found among those who took alcohol more than monthly, independent of former drinking, baseline risk and beverage choice. The hospitalization results were much like the mortality results for acute myocardial infarction.

In a previous study,²² lighter drinkers had a slightly lower noncardiovascular mortality risk than did the nondrinker reference group (including ex-drinkers). In the present study, lighter drinkers were at a similar risk as abstainers, and ex-drinkers at a higher noncardiovascular risk. This comparison suggests that the lower noncardiovascular but not the lower cardiovascular risk of lighter drinkers in the earlier study was spurious. It is clearly preferable to study ex-drinkers separately.

The disparate relation of alcohol to CAD from that of alcohol to most medical conditions, consistent in many studies, makes it unlikely that the inverse relation is spurious. Other features of the present study that argue that the alcohol-CAD relation is not spurious include: (1) independence from baseline CAD risk; (2) absence of higher CAD risk among persons reducing alcohol intake for medical reasons; (3) evidence that the higher unadjusted CAD risk of ex-drinkers is due to confounding covariates, mostly gender and smoking; (4) absence of a relation of CAD risk among ex-drinkers to maximal past intake; (5) absence of a relation of very light (<1/month) drinking to CAD risk; and (6) the similar reduction of CAD risk among drinkers of wine, liquor and beer.

Other conditions that shared with CAD a reduced risk of death among drinkers were occlusive cerebrovascular disease and nonspecific syndromes. The former has several risk factors in common with CAD; the latter presumably are the end results of CAD in many instances. Other reports 15,23,24 concerning alcohol and sudden cardiac death suggest an inverse relation. An inverse relation between alcohol intake and arterial stenoses, operative through blood lipid or antithrombotic effects of alcohol, or both, are plausible common operative factors in these findings.

There are some inconsistencies in the analyses of CAD subsets. Although chance variations in the subsets are possible owing to smaller numbers, we should attempt to explain the findings. Assuming that alcohol protects against CAD, is it plausible that women are more strongly protected than men? Our data with respect to alcohol and CAD in women are compatible with reports^{6,25-27} from other large cohorts. Increased

bioavailability of alcohol in women, owing to less gastric oxidation than occurs in men, could contribute to increased susceptibility to harmful effects of alcohol.²⁸ This phenomenon could translate into a greater protective effect at lower levels of alcohol intake in women. Thus, the greater sensitivity of women to the effects of alcohol on the liver^{6,29} might include an effect on HDL synthesis.

The reasons for the disparity between lifelong non-smokers (little alcohol-CAD relation) and the ex-smoker or current smoker groups is harder to explain. It could be difficult to demonstrate a weak alcohol-CAD relation in a low-risk group (persons who never smoked). It could also mean that nonsmokers who drink have less healthy dietary or exercise habits than do ex-smokers or smokers who drink. Yet another hypothetical explanation is that regular moderate alcohol consumption could specifically offset some harmful effect of smoking; for example, the effect of alcohol in raising HDL levels may be greater in smokers.³⁰

It remains possible that the lower CAD risk of lighter drinkers does not represent a protective effect. Lifelong abstainers could differ from drinkers in psychological traits, dietary habits, physical exercise habits or some other way that could be related to CAD risk. This and other studies indicate that such a correlate would need to be present in persons of both genders, in various countries and in multiple racial groups. While this is hypothetically possible, a causal protective effect of alcohol is a simpler and more plausible explanation.

These data should not be used to justify heavier drinking. The risk of death from all causes was highest among persons taking larger amounts of alcohol. Lighter drinkers (those taking up to 1 to 2 drinks/day) were at lowest risk of cardiovascular death and were not at higher risk of noncardiovascular death; such persons should not be advised to abstain for the purpose of lessening the risk of cardiovascular mortality. Health practitioners should advise concerned persons on an individual basis, taking into account the risk of uncontrolled drinking and of specific medical conditions. Problems associated with drinking make it unwise to advise abstainers indiscriminately to drink alcohol to reduce CAD risk.

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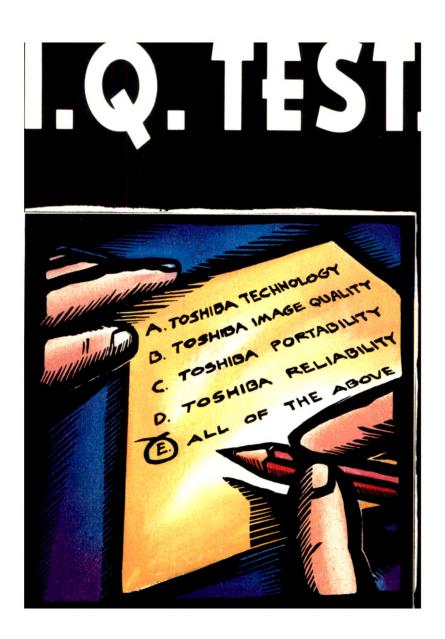
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Subnormal Parasympathetic Activity After Cardiac Transplantation

Michael L. Smith, PhD, Kenneth A. Ellenbogen, MD, Dwain L. Eckberg, MD, Helen M. Sheehan, BSN, and Marc D. Thames, MD

Heart period variability (standard deviation of 120 consecutive RR or PP intervals) was used to assess baseline parasympathetic activity in 18 patients with congestive heart failure before and after orthotopic cardiac transplantation, and was compared to that of 16 age-matched control subjects. Mean heart period variability (\pm standard error of the mean) was significantly greater (p <0.05) in control subjects (58 \pm 5 ms) than in the patients at any time before or after transplantation. Heart period variability of innervated recipient atria did not change significantly early (1 to 4 weeks) after transplantation (16 \pm 2 to 24 \pm 5 ms; p = 0.11), but increased significantly between weeks 15 and 37 after transplantation (30 \pm 5 ms, p <0.002 versus before transplantation). A stepwise regression model ($R^2 = 0.35$; p = 0.01) showed that heart period variability was directly related to time after transplantation and inversely related to systolic arterial pressure after transplantation and degree of rejection. Heart period variability of the denervated donor atria did not change from early to late periods after transplantation, suggesting that vagal reinnervation of the donor heart had not occurred. These data indicate that baseline parasympathetic activity does not increase significantly during the first month after transplantation but increases significantly between months 3 and 6.

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aseline parasympathetic activity and arterial baroreflex gain are attenuated in humans and experimental animals with congestive heart failure. 1-4 Ellenbogen et al⁵ showed that arterial baroreflex gain was normal in normotensive cardiac transplant patients. More recently, we found that baseline parasympathetic activity (heart period variability) was significantly greater in cardiac transplant patients than in heart failure patients, but remained subnormal.6 These previous data were derived from cross-sectional studies of different groups of patients. To date, a longitudinal study on the same patient cohort has not been used to assess directly the effect of cardiac transplantation on autonomic function. This study uses a longitudinal design to (1) determine if cardiac transplantation accounts for the improvement of baseline parasympathetic activity to the innervated recipient atria (suggested by the previous cross-sectional study); and (2) determine how changes in baseline parasympathetic activity after transplantation relate to changes in clinical parameters.

METHODS

Subjects: Eighteen men with congestive heart failure (aged 24 to 62 years, mean \pm standard error of the mean 46 ± 2) who underwent orthotopic cardiac transplantation were prospectively studied before and after this surgical procedure. Orthotopic cardiac transplantation was performed with techniques described previously. Each subject gave written informed consent. The study was approved by the Medical College of Virginia and Veterans Administration Hospital Committees on the Conduct of Human Research. Sixteen healthy agematched subjects free of organic heart disease were studied as control subjects.

Measurements: Measurements were obtained at the same time of day to avoid circadian variation. Patients with dyspnea or frequent (>4 beats/min) ventricular or atrial premature beats were excluded from the study. A standard limb lead rhythm strip was obtained in control subjects and patients before transplantation. An esophageal lead or intracavitary quadripolar catheter was used to record donor and recipient atrial activity in patients after transplantation. After 20 minutes of supine rest, an electrocardiographic rhythm strip was obtained for determination of mean PP interval and heart period variability. Rhythm strips were obtained from a stripchart recorder at a paper speed of 100 mm/s (accuracy ± 5 ms). Breathing rate was measured in 8 patients and was not significantly different between each measurement period.

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TABLE I Summary of Physiologic Data					
Group	PP Interval at Rest (ms)	Heart Period Variability (ms)	Systolic Pressure (mm Hg)		
Control (n = 16)	984 ± 39	58 ± 5	129±3		
Transplants (n = 18) Pretransplant, Recipient	760 ± 31	16±2	117±3		
Posttransplant,	782±36	24 ± 5*	132 ± 4*		
Recipient (early) Posttransplant, Recipient (late)	811 ± 45	30 ± 5*	145 ± 4*		
Posttransplant,	707 ± 34	6±1			
donor (early) Posttransplant, donor (late)	721 ± 28	7±1			

All values are mean ± standard error of the mean.

* Significantly different from values before transplantation (p <0.05).

Heart period variability was characterized as the standard deviation of 120 consecutive sinus rhythm PP intervals of the innervated recipient artia with a calibrated digitizing tablet (SigmaScan, Jandel Scientific). Measurement reliability was determined in 8 control subjects studied on 2 occasions, 7 days apart (paired t test). Heart period variability was unchanged in these subjects (day $0 = 41 \pm 7$ ms, day $7 = 39 \pm 6$ ms; p = 0.43).

Data analysis: Time of measurement was divided into 2 periods after transplantation: "Early" representing the first 4 weeks, and "Late" representing a period ranging from 15 to 37 weeks after transplantation. The data were normally distributed, and parametric analyses were performed. Pretransplantation and early or late posttransplantation were compared by analysis of variance with repeated-measures design and contrasts to discern differences between time periods. A probability <0.05 was considered significant. A stepwise regression analysis, with a model entry significance level of 0.25 was used to develop a model of pre- and posttransplantation clinical characteristics for the prediction of the

dependent heart period variability change from before to after transplantation. The independent variables tested for the model were time after transplantation, duration of class III/IV heart failure, ejection fraction before transplantation, degree of rejection at the time of study (on a 0 to 3 scale, where 0 = no rejection and 3 = severe rejection), systolic or diastolic arterial pressures after transplantation, and age. The model R² value represents the percent variation of the data explained by the model. The model R² was used to describe the statistical findings because it provides more succinct information about the model than the partial correlation coefficients.

RESULTS

All transplant patients received both cyclosporine and azathioprine as immunosuppressive therapy. The average duration of class III/IV heart failure and mean ejection fraction before transplantation was 6.6 ± 0.8 months (range 3 to 12) and $17.1 \pm 1.9\%$ (range 8 to 30), respectively.

Table I summarizes physiologic data for control subjects and for transplant patients for each measurement period in the transplant patients. Baseline PP interval $(984 \pm 39 \text{ ms})$ and heart period variability $(58 \pm 5 \text{ ms})$ was significantly greater in control subjects than in transplant patients at any period. Neither recipient PF intervals nor donor P'P' intervals of transplant patients changed (p > 0.05) after transplantation. Arterial pressure increased significantly during the first month after transplantation (p = 0.01) and increased further during the late measurement period (p = 0.04).

Mean heart period variability of the control group was significantly greater than that of all other groups Heart period variability of the innervated recipient atria of the transplant patients (Table I) did not increase significantly by the early posttransplantation study (p = 0.11), but did increase significantly by the late study (p = 0.02 compared to early posttransplantation; p = 0.002 compared to before transplantation). Three patients showed dramatic increases in heart period variables.

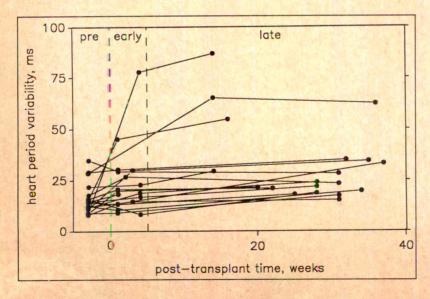


FIGURE 1. Individual heart period variability data for each patient before (pre), during the first 4 weeks (early) and during weeks 15 to 37 (late).

ability. The analyses were repeated excluding these patients to determine if differences before and after transplantation were attributable to these patients alone. Heart period variability increased from 15 ± 2 to 17 ± 4 ms between pre- and early posttransplantation (p = 0.17), and to 24 ± 3 ms at late posttransplantation (p = 0.003) in the 15 patients. Heart period variability of the denervated donor atria was unchanged from early to late posttransplantation (p = 0.79).

Heart period variability of recipient atria was widely distributed after transplantation. Individual data before and after transplantation are illustrated in Figure 1. Stepwise regression analyses were performed to determine clinical and physiologic correlates of heart period variability changes associated with cardiac transplantation. A significant model was obtained in which time after transplantation was directly related, and systolic arterial pressure and degree of rejection were inversely related to the change in heart period variability. The model, although significant, was a poor predictor of heart period variability ($R^2 = 0.35$, p = 0.01).

DISCUSSION

Previously, we reported on cross-sectional comparisons in which baroreflex gain is normal and heart period variability is near normal in cardiac transplant patients. 5,6 The present study is the first longitudinal study of the effect of cardiac transplantation on baseline parasympathetic activity. Our data show that heart period variability of innervated recipient atria of transplant patients, used as an index of baseline parasympathetic activity, can increase after cardiac transplantation, but usually remains subnormal. The degree of restoration of heart period variability is inversely related, in part, to arterial pressure after transplantation and the degree of rejection. These data suggest that baseline parasympathetic activity improves, but usually does not return to normal after cardiac transplantation.

We used heart period variability during quiet breathing to assess baseline cardiac parasympathetic activity in humans. This measure is considered a reasonable estimate of parasympathetic activity when respiration is regular and physiologic conditions are stable. Baseline levels and changes of heart period variability are related directly to cardiac parasympathetic efferent nerve activity in dogs. The heart period variability measure used in the present study, standard deviation of PP interval, correlates with other measures of cardiac parasympathetic activity; therefore, this measure is a simple, yet powerful estimate of baseline parasympathetic activity.

Parasympathetic activity in heart failure before transplantation: Reduced baseline parasympathetic activity and arterial baroreflex gain, ¹⁻³ elevated baseline parasympathetic activity and elevated plasma norepinephrine concentration^{10,11} are hallmarks of congestive heart failure. Furthermore, cardiac parasympathetic activity is related inversely to the severity of heart failure and prognosis of heart disease. ^{1,12,13} Our patients had profoundly subnormal heart period variability associated with heart failure before transplantation, suggest-

ing a severe abnormality of baseline parasympathetic activity (Figure 1). These findings support previous reports of reduced parasympathetic activity in congestive heart failure.^{1,2}

Parasympathetic activity after transplantation: Heart period variability of the innervated recipient atria did not increase significantly during the first month after transplantation, but increased significantly between weeks 15 and 37 (late posttransplant period). However, only 4 of the 18 patients showed increases >10 ms; thus, these data suggest that heart period variability does not necessarily improve after transplantation. In our previous cross-sectional study,6 a diverse patient population was studied with posttransplant time ranging from 2 weeks to 5 years. Those data suggested that heart period variability increased substantially after transplantation and continued to increase progressively over time. However, few patients were studied in the first 6 weeks after transplantation. The present data support the previous study in showing that an increase in heart period variability usually occurs with time after transplantation. However, these data also show that the improvement is delayed and is not usually very dramatic.

Ellenbogen et al⁵ reported that arterial baroreflex gain is normal in transplant patients. Their findings imply normal parasympathetic responsiveness in the presence of impaired baseline parasympathetic activity. Therefore, we hypothesize that the subnormal baseline activity is not due to an impairment along the efferent vagal pathway; rather, it is best explained by a change in the total afferent input to the cardiac vagal motor nuclei in the brain.

A stepwise regression model indicated that changes in heart period variability after transplantation correlate directly with time after transplant, and inversely with systolic arterial pressure and degree of rejection. This analysis supports the hypothesis that heart period variability tends to increase with time after transplantation. Furthermore, these data support our previous conclusion⁶ that hypertension after transplantation adversely affects baseline parasympathetic activity. However, the predictive power of the model ($R^2 = 0.35$) was poor, indicating that other factors confound the measurement of heart period variability after cardiac transplantation. Other factors probably contributed to the variation of responses: (1) Patients were receiving a variety of medications that could affect parasympathetic activity; and (2) the rates of patient recovery from cardiac transplantation are highly individual and difficult to assess.

Heart period variability in denervated donor atria: The denervated donor hearts of the transplant patients demonstrated minimal heart period variability, consistent with previous reports of little or no respiratory sinus arrhythmia in such patients. 14,15 This lack of heart period variability suggests that parasympathetic reinnervation of the heart does not occur during the first 6 months after transplantation. Reinnervation occurs as early as 2 months 16 and autonomic innervation appears to be functionally effective within 9 months 17 in autotransplanted dogs. However, in human transplant pa-

tients, evidence from heart period variability⁶ and heart rate responses to exercise¹⁴ suggest that no reinnervation occurs during the first 2 years after transplantation. Fallen et al¹⁸ recently showed that the power spectrum of heart rate variability of 1 transplant patient was normal, including both low frequency and respiratory peaks, at 33 months after transplantation. This finding is indicative of normal parasympathetic innervation of the heart. This is the only isolated finding of possible reinnervation in humans of which we are aware.

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Natural History of Cardiac Rhabdomyoma in Infancy and Childhood

John F. Smythe, MD, John D. Dyck, MD, Jeffrey F. Smallhorn, MD, and Robert M. Freedom, MD

Although spontaneous regression of cardiac rhabdomyoma has been reported, prognosis is still considered to be poor and surgery continues to be indicated. The experience with rhabdomyoma diagnosed in live infants over a 20-year period was reviewed. Diagnosis by angiography or echocardiography was accepted only if multiple tumors were present or if tuberous sclerosis was also diagnosed. Nine patients (3 diagnosed prenatally and the remaining 6 at age <8 months) were identified as having a total of 24 tumors. Measurements in 2 planes demonstrated at least some evidence of regression in 24 patients (100%), with 20 of 24 having complete resolution. One patient required delayed surgery for excision of a subaortic ridge that appeared at the site of a resolved tumor. Our findings suggest that pediatric cardiac rhabdomyoma is most often a benign condition in which spontaneous regression is the rule. Surgery is recommended only for patients with refractory dysrhythmias or severe hemodynamic compromise.

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ardiac rhabdomyoma, while rare at all ages, is the most common primary cardiac tumor in infancy and childhood. This tumor first described in 18622 has been demonstrated to have a clear association with the neurocutaneous syndrome known as tuberous sclerosis.3 The majority of the reports dealing with this tumor are autopsy series. 4,5 The few reports of this tumor in live patients suggest that the outlook is poor and that death within the first 5 years of life is usual.⁶⁻⁸ A number of investigators have therefore suggested that an aggressive surgical approach to this tumor is indicated.5,9-11 Recently, published reports have described spontaneous regression of cardiac rhabdomyomas. 11,12 To date, the natural history of this unusual cardiac problem remains unclear.

We review our experience over a 20-year period with cardiac rhabdomyoma diagnosed in living patients during infancy and childhood.

METHODS

The hospital records, angiograms and 2-dimensional ultrasound evaluations of all patients entered into the cardiac record with the diagnosis of cardiac rhabdomyoma during life, between the years 1969 and 1989, were reviewed. To be certain that all patients selected did indeed have this tumor the following criteria for acceptance into the study were established: demonstration of the presence of multiple intracardiac masses with characteristic echocardiographic or angiographic appearance, in the absence of known malignant disease; or existence of 1 or more tumors in association with the neurocutaneous syndrome of tuberous sclerosis.

These criteria were based on the information that fibromas and myxomas (other primary cardiac tumors occasionally seen in childhood) are invariably solitary tumors,13 and on the very strong association between rhabdomyomas and tuberous sclerosis.3,13 We believe that these criteria ensured that all patients entered into the study had rhabdomyomas exclusively.

Angiograms and ultrasound evaluations were reviewed separately by 2 cardiologists with training in these imaging techniques. Note was made of tumor position in the cases of multiple tumors. Follow-up studies of the identified tumors were classified on the basis of size as demonstrating a given tumor to be (1) increased, (2) unchanged, (3) partially resolved, and (4) completely resolved. Tumors that did not undergo complete resolution had their areas in 2 planes measured with a Sony® Offline Ultrasound Analysis System to objectively confirm the observations of the cardiologists. In all

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TABLE I Patient Characteristics and Tumor Outcome

Case Sex/Age			Tumor Location				Follow Up	Status
	Sex/Age	Presentation	RA	RV	LV	IVS	Follow-Up (regression)	(clinical)
1	M/7 mo	Arrhythmia		L. Transport	1		1/1	Alive/TS
2	F/2 days	Arrhythmia				1	1/1	Alive/TS
3	M/3 mo	Murmur		1	1		2/2	Alive/TS
4	F/2 days	Murmur			1		1/1	Alive/TS
5	M/3 days	Murmur			1	1	1/2	Alive
6	F/prenat.	Screening U/S	1		2	2	4/5	Alive/TS
7	M/prenat.	Arrhythmia	1	2	2		5/5	Alive/TS
8	F/1 day	Murmur	2		2	1	4/5	Sub AS-S
9	F/prenat.	FHxTS			1	1	1/2	Alive/TS

Regression denotes complete resolution. FH = family history; IVS = interventricula TS = tuberous sclerosis; U/S = ultrasound. ar septum; LV = left ventricle; prenat. = prenatal; RA = right atrium; RV = right ventricle; Sub As-Sx = subaortic stenosis-surgical resection;

cases there was complete concordance between the observations of the 2 cardiologists and between the cardiologists and the analysis system.

In an effort to determine if the true incidence of rhabdomyoma in infancy and childhood was changing, a review of autopsy records at the Hospital for Sick Children was conducted for 2 consecutive periods. The number of cases having this tumor identified at autopsy between 1919 and 1969 was compared with the number identified between 1969 and 1989. The number for each period was compared with the total number of patients seen at the Hospital for Sick Children, Toronto, over the same time periods.

RESULTS

Eleven patients (6 men and 5 women) who fulfilled the diagnostic criteria were identified over the 20-year period from January 1969 to January 1989. Of these, 1 patient died at 1 day of age of unrelated anomalies. Nine of the remaining 10 have been followed for at least 1 year and constitute our study population. Seven

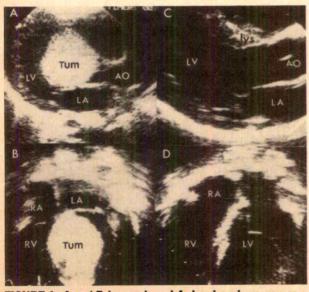


FIGURE 1. A and B, long-axis and 4-chamber views, respectively, of patient 5 at age 16 months. C and D, same patient at 57 months. AO = aorta; LA = left atrium; LV = left ventricle: RA = right atrium; RV = right ventricle; Tum = tumor.

patients (78%) were followed with the diagnosis of tuberous sclerosis. In 3 patients the initial diagnostic study was angiographic, with all other studies being echocardiographic. Table I summarizes the pertinent clinical data and investigations on all patients.

Three patients were initially identified at the time of fetal cardiac ultrasound examination (Table I). These examinations had been performed because of fetal tachycardia, family history of tuberous sclerosis, and an abnormality detected on a level 2 obstetric ultrasound evaluation. Among the remaining 6 patients detected after birth, 2 presented with dysrhythmias, 2 with asymptomatic cardiac murmurs and 2 with cardiac murmurs in the setting of tuberous sclerosis.

Mean period of follow-up was 7 years (range 1.9 to 15.3). Spontaneous regression, either complete or partial, was observed in all cases. Figure 1 is a representative example (case 5). Of a total of 24 tumors identified, 20 underwent complete regression, and 3 partial regression, which by area measurement exceeded 50%. One tumor (Table I, case 9) at 2 years of follow-up had decreased in size by only 30% according to area measure-

One patient (case 8) developed a significant subaortic fibrous diaphragm at the precise site of a resolved rhabdomyoma. The surgical resection specimen failed to demonstrate any evidence of residual tumor. None of the other patients required surgical intervention and all are currently alive without cardiac symptomatology.

Between 1919 and 1969 a total number of 6 cases of rhabdomyoma were diagnosed at autopsy, whereas between 1969 and 1989 a single case was diagnosed at autopsy. The incidence of cardiac rhabdomyoma has therefore not undergone a significant change between these 2 time intervals.

DISCUSSION

Histologic proof of the diagnosis of rhabdomyoma is no longer considered necessary in the presence of characteristic echocardiographic findings. 14 Rhabdomyomas are usually multiple and frequently lobulated. They arise most often in the interventricular septum but some 30% will have atrial wall involvement.4 These features plus the strong association with tuberous sclerosis facilitate noninvasive diagnosis. 14 The advent and widespread

use of 2-dimensional echocardiography^{8,14,16} (supplanting angiography as the principal diagnostic method) and, more recently, the broad application of the ultrasound technique to screening of fetal cardiac anatomy, 15,16 had undoubtedly led to the earlier and more frequent diagnosis of cardiac rhabdomyoma in asymptomatic cases. Certainly, the cases reported here were far less symptomatic at the time of diagnosis than those reported by others. 1,6,8 Review of our records and autopsy material suggests that the true incidence of cardiac rhabdomyoma is probably not changing but that the detection rate for this tumor must be increasing. It is only recently, therefore, that an accurate appraisal of the natural history of this lesion can be made. The value of magnetic resonance imaging in assessing intracardiac masses has been reported,17 and this method may also assist in charting the course of these lesions.

Symptoms resulting from cardiac rhabdomyomas are largely a consequence of tumor size or location within the heart. Inflow or outflow tract obstruction may lead to myocardial dysfunction with resultant congestion or cyanosis. Refractory cardiac dysrhythmias and systemic embolization are other events that will bring patients to medical attention. It is apparent that symptomatic patients may have a poor outlook without intervention, which has prompted the advocacy of early

and aggressive surgery by some workers. 5,9-11

In 1975, spontaneous regression of a cardiac rhabdomyoma was reported.11 Subsequently, others have advocated an expectant approach to management.14 Nevertheless, the strength of the case for or against aggressive management remains unresolved. Our study certainly demonstrates that spontaneous tumor regression is overwhelmingly the rule and that in the absence of lifethreatening complications conservative management is probably indicated.

A review of published reports revealed 15 cases of rhabdomyoma with at least some evidence of tumor regression. 1,12,14,18-25 Nevertheless, the question of whether aggressive surgical management is indicated in all cases remains unresolved. Our study documents that with a large number of patients followed in a single center, cardiac rhabdomyoma, while occasionally lifethreatening, is increasingly diagnosed in patients with few or no symptoms. This suggests that the tumor may in fact have a greater incidence than previously appreciated. Furthermore, spontaneous regression of most, if not all, tumors over several years can be anticipated, to the extent that an expectant approach to management is

clearly advisable in the absence of life-threatening symptoms.

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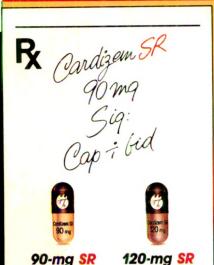
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capsules

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second-or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by x-ray

capsules

WARNINGS

- Transmiss 1. Cardiac Conduction. CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (nine of 2,111 patients or 0,43%). Concomitant use of dilitazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to
- 5 seconds) after a single dose of 60 mg of diffiazem.
 2. Congestive Heart Failure. Although diffiazem has a negative inotropic effect in solated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral dittazem in patients with impaired ventricular function (ejection fraction $24\% \pm 6\%$) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Experience with the use of CARDIZEM (diltiazem hydrochloride) in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.
- 3. Hypotension. Decreases in blood pressure associated with CARDIZEM therapy
- hypotension. Decreases in blood pressure associated with Chronical metaly may occasionally result in symptomatic hypotension.

 Acute Hepatic Injury. Mild elevations of transaminases with and without concomitant elevation in alkaline phosphatase and biliniubin have boserved in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1 to 8 weeks) and have been reversible upon discontinuation of drug therapy The relationship to CARDIZEM is uncertain in some cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with imparater fand or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued in dogs doses of 22 mg/kg are sign associated with

the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing. Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be

Drug Interaction. Due to the potential for additive effects, caution and careful ration are warranted in patients receiving CARDIZEM concomitantly with any agents known to affect cardiac contractifity and/or conduction. (See WARRINGS.)
Pharmacologic studies indicate that there may be additive effects in prolonging
AV conduction when using beta-blockers or digitalis concomitantly with
CARDIZEM. (See WARRINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly admin-istered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of CARDIZEM (diltiazem hydrochloride) concomitantly propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50% if combination therapy is initiated or withdrawn in conjunction with proprandlol an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

an adjustment in the proprantor dose may be warranted. (See WAKNINGS.)

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Neither Administration of CARDIZEM with digory in 124 healthy, male sub-

Digitalis: Administration of CARDIZEM with digoxin in 24 healthy buggtants: Administration of CARDIZEM with digion in 24 heariny male sub-jects increased plasma digioxin concentrations approximately 20%. Another investigator found no increase in digioxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digioxin levels, it is recommended that digioxin levels be monitored when initiat-ing, adjusting, and discontinuing CARDIZEM therapy to avoid possible over-or under-digitalization. (See WARNINGS.)

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic respo fertility was observed in rats. onse in in vitro bacterial tests. No intrinsic effect on

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in ton a lings basis) with the dairy elementated with perfect of the dairy of the dair

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should

Pediatric Use. Safety and effectiveness in children have not been established

ADVERSE REACTIONS

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies. The adverse events described below represent events observed in clinical studies of hypertensive patients receiving either CARDIZEM Tablets or CARDIZEMS Capsules as well as experiences observed in studies of angina and during marketing. The most common events in hypertension studies are shown in a table with rates in placebo patients shown for comparison. Less common events are listed by body system; these include any adverse reactions seen in agains. table with rates in placebo patients shown for comparison. Less common events are listed by body system; these include any adverse reactions seen in angina studies that were not observed in hypertension studies. In all hypertensive patients studied (over 900), the most common adverse events were deema (19%), headache (83%), dizziness (6%), asthenia (5%), sinus bradycardia (3%), flushing (3%), and 1° AV block (3%). Only edema and perhaps bradycardia and dizziness were dose related. The most common events observed in clinical studies (over 2,100 patients) of angina patients and hypertensive patients receiving CARDIZEM Tablets or CARDIZEM SR Capsules were (ie, greater than 1%) edema (5.4%), headache (4.5%), dizziness (3.4%), asthenia first-degree AV block (1.8%), flushing (1.7%), nausea (1.6%), bra (1.5%), a

nd rash (1.5%).		
	BLIND PLACEBO CONTROL Ypertension trials	LED
	Diltiazem	P

HYP		
Adverse	Diltiazem N=315 # pts (%)	Placet N=21 # pts (
headache	38 (12%)	17 (8%
AV block first degree	24 (7.6%)	4 (1.99
dizziness	22 (7%)	6 (2.89
edema	19 (6%)	2 (0.99
bradycardia	19 (6%)	3 (1.4
ECG abnormality	13 (4.1%)	3 (1.4
asthenia	10 (3.2%)	1 (0.5
constipation	5 (1.6%)	2 (0.9
dyspepsia	4 (1.3%)	1 (0.5
nausea	4 (1.3%)	2 (0.9
palpitations	4 (1.3%)	2 (0.9
polyuria	4 (1.3%)	2 (0.9
somnolence	4 (1.3%)	_
alk phos increase	3 (1%)	1 (0.5
hypotension	3 (1%)	1 (0.5
insomnia	3 (1%)	1 (0.5
rash	3 (1%)	1 (0.5
AV block second degree	2 (0.6%)	_

In addition, the following events were reported infrequently (less that have been observed in angina trials. In many cases, the relation to

Cardiovascular: Angina, arrhythmia, bundle branch block, tachycai tricular extrasystoles, congestive heart failure, synct
Nervous System: Amnesia, depression, gait abnormality, hallucinati
vousness, paresthesia, personality change, tinnitu:

abnormal dreams. Gastrointestinal: Anorexia, diarrhea, dysgeusia, mild elevations of SG and LDH (see hepatic warnings), vomiting, weight

Dermatological: Petechiae, pruritus, photosensitivity, urticaria.

Ambiyopia, CPK increase, dyspnea, epistaxis, eye hyperglycemia, sexual difficulties, nasal congestion, ostewarticular pain, impotence, dry mouth.

The following postmarketing events have been reported infrequentients receiving CARDL/EM-alopecia, gingival hyperplasia, erythema m and leukopenia. Definitive cause and effect relationship between the and CARDL/EM therapy cannot yet be established.

0



Is the Term "Tricuspid Atresia" Appropriate?

P. Syamasundar Rao, MD

The term "tricuspid atresia" has most frequently been defined as the congenital absence or agenesis of the morphologic tricuspid valve. 1,2 In the nineteenth century3,4 and in the early twentieth century,5 long descriptive names were used for this anomaly. The twentieth century term "tricuspid atresia" has been in common usage,3,4 is almost exclusively used in textbooks,² and is short and simple. Furthermore, the term connotes a true pathologic and clinical entity as it is visualized by most cardiologists, surgeons and pathologists. 1-4 There has been a debate with regard to terminology between Bharati and Lev versus Anderson et al.6-12 I favored the old term "tricuspid atresia" and stated the reasons for such conclusions previously.^{1,2} I was repeatedly criticized¹³⁻¹⁶ for taking that position. Recently, further evidence¹⁷ became available that will reaffirm my belief. This communication discusses the problem and the appropriateness of using the term "tricuspid atresia" to describe the congenital absence or agenesis of the morphologic tricuspid valve.

THE CONTROVERSY

Bharati et al⁷ in 1976 reported their anatomic observations of 416 hearts with tricuspid atresia or stenosis and commented that tricuspid atresia with or without transposition of the great arteries is distinctly different from the single (primitive) ventricle with a small outlet chamber and outlined the reasons for their conclusion. Anderson et al⁸ took issue with Bharati et al's interpretation that tricuspid atresia is not a variant of the primitive (single) ventricle and the controversy began and the arguments continued.9-12 Anderson et al6,18 attempted to distinguish between occluded (or imperforate) tricuspid valve and absent tricuspid valve and interjected the term "univentricular heart" to describe both tricuspid atresia and the single ventricle and were just short of suggesting that the term tricuspid atresia be reserved for the rare condition 19,20 with well-formed but fused tricuspid valve leaflets; but they came around to agree to use the term "classical tricuspid atresia" to describe the heart with what they call univentricular heart of left ventricular type with absent right atrioventricular connection in situs solitus. I and others^{2,9,10,12,21,22} had difficulty in agreeing to this univentricular heart concept.

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THE ARGUMENTS

Anderson contended (initially)^{6,8,11} that the inflow portion is absent in tricuspid atresia, and therefore the chamber under consideration is not a right ventricle; furthermore, he suggested that this chamber is similar to the outlet chamber of the single ventricle. Therefore, tricuspid atresia and the single ventricle are univentricular hearts. Bharati and Lev9,10 admitted that there usually is no tricuspid tensor apparatus in the right ventricle of tricuspid atresia, but found a distinct area beneath perital and septal bands, which they call sinus. In cases in which this is not grossly visible (particularly in cases with associated d-transposition of the great arteries), they confirmed its presence histologically.9

Anderson argued that the architecture of the left ventricle in tricuspid atresia and the main chamber in the single ventricle are similar and comparable, 6,8 whereas Bharati and Lev7,9,10 felt that the tricuspid atresia left ventricle is clearly a morphologic left ventricle despite occasional abnormalities, and that the main chamber of the single ventricle is bizarre. Furthermore, they observed that the atrioventricular valve of the left ventricle in tricuspid atresia is morphologically a mitral valve, whereas the atrioventricular valves in the single ventricle resemble each other and that no differentiation between tricuspid and mitral valve can be made. 10

Bharati and Lev found that the anterior and posterior descending coronary arteries meet in the apical region in tricuspid atresia and demarcate right and left ventricles, whereas the coronary arteries do not do so in the single ventricle. 7,9,10 Anderson's observations suggested that coronary arterial pattern was similar in both the lesions. 6,8

There is unanimity of the findings of the conduction systems between both groups but the interpretations were different. Anderson contends they are similar. Bharati and Lev feel strongly that they are different posteriorly placed atrioventricular node and conduction system in tricuspid atresia and anteriorly placed conduction system in the single ventricle.

Rosenquist et al²³ studied 14 tricuspid atresia specimens by transillumination and found that the presumed site of the atretic tricuspid valve transmitted the light into the left ventricle in all 14 cases. Anderson et al^{6,8} cite this and the evidence from his own dissection and microscopic studies, showing a potential communication of the atretic right atrial orifice with the left ventricle, and suggesting that tricuspid atresia is a variant of the single ventricle. Bharati and Lev's defense is that secondary hemodynamic changes after the first 2 months of gestation could place the atretic tricuspid valve anywhere, and that therefore this argument is not valid.

TABLE I Comparison of Prevalence of Great Artery Relations in Tricuspid Atresia and Double Inlet Left Ventricle

	Tricuspid Atresia* No. (%)	Double Inlet Left Ventricle† No. (%)	p Value
Total number	653	189	THE
Normally related great arteries	478 (73)	32 (17)	<0.005
Transposition of the great arteries	175 (27)	157 (83)	<0.005
d-transposition	156 (24)	73 (39)	< 0.005
I-transposition	19 (35)	84 (44)	< 0.005

In addition to the objections cited by Bharati and Lev that I listed earlier and with which I agree, there are other problems, as pointed out by Gessner.²⁴ In tricuspid atresia most hearts demonstrate normally related great arteries,²⁵ whereas most hearts with a single ventricle (double inlet left ventricle with 2 atrioventricular valves) exhibit transposition of the great arteries.^{26–29} When transposition of the great arteries is present, even the type of transposition, 1- or d-transposition, is different for these 2 lesions (Table I). Therefore, it would seem that there is a fundamental difference in the evolution of these 2 entities.

The electrovectorcardiographic patterns are different for these 2 conditions: The QRS vector (axis) in the frontal plane is directed to the left and is superior in most cases of tricuspid atresia, while the frontal plane QRS vector in the double inlet left ventricle is directed to the left and inferiorly, again suggesting the difference between these 2 conditions.

Finally, when Gessner³¹ experimentally produced a double inlet left ventricle by mechanical interference in chick embryos, no instances of tricuspid atresia or even

of tricuspid valve hypoplasia were seen, again suggesting dissimilarities between these 2 entities.

A CHANGE OF MIND

More recently. Anderson et al14,32 retracted some of the univentricular heart concepts by making statements such as, "We erred when we described the included lesions as univentricular hearts" and "When we used the term univentricular heart, we were fully aware that most of the hearts thus described possessed 2 ventricular chambers. We attempted to counter this lack of logic by our definition of ventricles. But.... We have now resolved the matter simply by expunging the inappropriate use of 'univentricular' from our system." They then introduced the concept of univentricular atrioventricular connection. 14,32 It appears that they have done this in an attempt to group together all those hearts with atria connected to only 1 ventricle in contradistinction to those hearts in which each atrium is connected to its own ventricle.32 They included tricuspid atresia as 1 of the entities under the umbrella of univentricular atrioventricular connection.

THE RESOLVE

In my opinion neither the tricuspid atresia hearts with well-formed but fused tricuspid valve leaflets (called imperforate tricuspid valve by Anderson) nor the classic tricuspid atresia hearts (the muscular variety) with a dimple or a localized fibrous thickening in the floor of the right atrium (called absent right atrioventricular connection by Anderson) belong to the univentricular atrioventricular connection group. Anderson et al^{6,8,18} stated that the rare form^{19,20} of tricuspid atresia with well-formed but fused tricuspid valve leaflets has a biventricular connection; I agree, and this issue will not be discussed further. The more common muscular variety, the classic tricuspid atresia, is what I will be

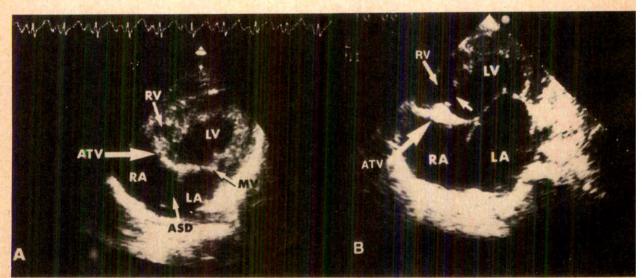


FIGURE 1. Subcostal 4-chamber 2-dimensional echocardiographic views of the heart in 2 children with tricuspid atresia. Note dense band of echoes representing atretic tricuspid valve (ATV) (large arrows) overlying the right ventricular (RV) cavity, although part of the ATV covers the left ventricular (LV) cavity. The left atrium (LA) and right atrium (RA) are also shown. A, an atrial septal defect (ASD) is seen, whereas, in B, there is a ventricular septal defect (small arrow). These echocardiographic figures demonstrate that the atretic tricuspid valve is related to the right ventricle. MV = mitral valve.

discussing. An excellent study of Wenink and Ottenkamp¹⁷ sheds some light on the issue at hand. They found a tiny inlet portion in addition to the trabecular portion on gross examination of the morphologic right ventricle in 10 of 31 classic tricuspid atresia hearts studied. Serial sectioning of 2 of these hearts showed a fibrous remnant in continuity with the central fibrous body; this fibrous remnant was present not only above the left ventricle but also above the right ventricle.17 The microscopic examination also confirmed that the right ventricle had a hypoplastic inlet portion.¹⁷ These data suggest that the so-called absent right connection did indeed show a connection between the right ventricle and right atrium. The findings of these authors are of great significance in the understanding of the morphogenesis of tricuspid atresia and in providing proof that the atretic tricuspid valve was indeed related to the right ventricular inflow portion. This then becomes an occluded or imperforate right atrioventricular (tricuspid) valve and not absent right atrioventricular connection. These findings are further supported by our echocardiographic observation^{2,33} and that of others,^{34,35} where the atretic tricuspid valve overlying the hypoplastic right ventricular cavity is clearly seen (Figure 1).

It may be surmised that after division of the atrioventricular canal, the atrioventricular orifice becomes atretic, perhaps due to fusion of its components.²⁴ The hypoplasia of the right ventricle may be related either to restriction of flow into it, because of inlet valve atresia, or to concomitant malalignment of the ventricular loop with the atrioventricular canal.36 Whether a muscular type of tricuspid atresia develops or well-developed but fused tricuspid valve leaflets develop depends upon the stage of development at which the embryologic abnormality takes place; the muscular form of tricuspid atresia develops if the embryologic abnormality occurs in very early gestation, and better-formed but fused valve leaflets occur if these embryologic abnormalities occur slightly later in gestation. If the valve fusion is incomplete, tricuspid valve stenosis develops. The pathologic,7 clinical33,37 and electrocardiographic37 features of this lesion and tricuspid atresia are similar, and therefore it is not surprising that isolated tricuspid stenosis belongs to the group of tricuspid atresia and that their embryologic development is similar. Thus, the tricuspid valve stenosis, tricuspid atresia with well-developed but fused valve leaflets and the muscular type of tricuspid atresia represent a spectrum of morphologic abnormality; the type of outcome depends upon the time of onset of embryologic abnormality.

In summary, gross and microscopic findings reported by Wenink and Ottenkamp and echocardiographic evidence strongly support the idea that tricuspid atresia is not an example of univentricular atrioventricular connection and that there is biventricular concordant connection in cases with tricuspid atresia. Our own observations during the course of many studies on tricuspid atresia and the single ventricle, ^{2,19,38–40} and unpublished observations of many angiograms and pathologic specimens of many patients with tricuspid atresia and a single ventricle made at several institutions where the au-

thor has had the privilege to work, suggest that the 2 entities are clearly different. Furthermore, these lesions are hemodynamically and surgically different. Because of these reasons we should continue to use the term tricuspid atresia as it has been used in the past. It is concluded that the term tricuspid atresia is indeed the correct and logical term to describe this disease entity.

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Supported Coronary Angioplasty and Standby Supported Coronary Angioplasty for High-Risk Coronary Artery Disease

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espite advances in technology and experience, there continues to be an appreciable acute closure rate¹⁻³ associated with percutaneous transluminal coronary angioplasty (PTCA). Hemodynamic compromise may also occur when a wire or balloon is advanced across or inflated in a strategically located vessel. Therefore, in high-risk patients, techniques are necessary to enable support of the coronary or systemic circulation, or both, should hemodynamic collapse occur. Prophylactic coronary support strategies have included coronary sinus retroperfusion⁴ and regional coronary perfusion of blood^{5,6} or oxygenated fluorocarbons.7 The intraaortic balloon pump8 and percutaneous cardiopulmonary bypass^{9,10} have been advocated to support the systemic circulation during high-risk interventional procedures or crises during more routine invasive procedures.

The purpose of this report was to relate our experience using supported coronary angioplasty (PTCA with percutaneous cardiopulmonary bypass) and to compare it to a similar group of patients undergoing PTCA when the cardiopulmonary bypass system was not inserted but used as standby. This comparison will serve to (1) describe morbidity of these procedures, (2) define indications for percutaneous cardiopulmonary bypass use during PTCA, and (3) demonstrate the safety of expectant percutaneous cardiopulmonary bypass use.

Since December 1987, we have used supported angioplasty (S-PTCA) for very high-risk patients undergoing PTCA. S-PTCA utilizes percutaneous cardiopulmonary bypass initiated prophylactically before performance of coronary angioplasty. We have also performed PTCA on a clinically and angiographically similar group of patients who were evaluated and prepared for percutaneous cardiopulmonary bypass, but the cannulas were inserted only in the event of hemodynamic collapse. We have termed this latter group standby supported angioplasty (SB-PTCA). The patients underwent angiographic evaluation and instrumentation of the contralateral (to the PTCA site) femoral artery and vein with small bore catheters, with percutaneous cardiopulmonary bypass equipment and personnel available.

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Definition of high-risk coronary artery disease was the same in both PTCA and SB-PTCA groups: (1) severe or unstable angina with ≥1 approachable target vessels with ≥75% diameter stenosis, and left ventricular ejection fraction ≤25%, or (2) >50% of the viable left ventricular myocardium jeopardized by a target lesion.

Anginal symptoms were graded according to the Canadian Heart Association classification. Heart failure was graded according to the New York Heart Association classification. The percent luminal diameter stenosis was determined visually using a caliper and comparing the target lesion to a proximal segment judged representative of "normal" caliber. Left ventricular ejection fraction was determined by contrast or radionuclide angiography. The extent of territory supplied by the target

TABLE I Comparison of Patients Undergoing Supported and Standby Supported Angioplasty

	Supported Angioplasty	Standby Supported Angioplasty	p Value
No. of pts.	14	13	
Age (yrs)	58 ± 11	66 ± 12	< 0.05
Sex	12 men	9 men	
Angina			
class* III	2	1	
class IV	12	12	NS
CHF Class†			
≥	7	5	
≤	7	8	NS
LVEF(%)	26 ± 13	26±9	NS
No. of coronary arteries			
narrowed >50% in diameter		ALC: Train	
Three	7	7	
Two	4	5	
One	1		
LMCA	2	1	NS
Vessels attempted	18	13	
Successful	16	13	1404
% Stenosis	00.5/	00.44	***
Pre/post	93±5/	92±4/	NS
	25 ± 15	24±8	NIC
Mortality			NS
Procedural	2	0	
Late	0	1	NS
Morbidity Transfusion	8	1	INS
GI bleed	1	0	
Femoral vein	1	0	2 mark to the
thrombosis	STEEL STATE		
Femoral bleed	1	0	
Late reocclusion	1	0	100
Late reocciusion		0	TO THE TANK

Canadian Heart Association class New York Heart Association class.

CHF = congestive heart failure; GI = gastrointestinal; LMCA = left main coronary artery dilated; LVEF = left ventricular ejection fraction; NS = not significant; PTCA = percutaneous transluminal coronary angioplasty.

vessel was determined by consensus of 2 angiographers. In all cases where the indication was >50% of the myocardium jeopardized, the target vessel supplied collaterals to another coronary artery with a proximal chronic total occlusion considered not amenable to balloon PTCA. These indications were based on the likelihood of hemodynamic collapse occurring should flow in the vessel cease by acute closure or during balloon inflation.

Our experience detailed in this report reflects consecutive, not randomized, patients during our initial experience with S-PTCA. When the significant morbidity associated with insertion of the cannulas was recognized, we switched to a strategy of SB-PTCA in the subsequent consecutive patients with similar indications.

Data are reported as mean ± standard deviation.

Statistical analysis comparing data from S-PTCA and SB-PTCA groups was done using Student's t test and the chi-square method. A p value < 0.05 was considered statistically significant.

Fourteen parients (12 men and 2 women, mean age ± standard deviation 58 ± 11 years) underwent S-PTCA. Results are listed in Table I.

The SB-PTCA group consisted of 13 patients (9 men and 4 women, mean age \pm standard deviation 68 \pm 11, p <0.05; difference not significant [NS]).

Twelve patients in the S-PTCA group had Canadian Heart Association class IV and 2 patients class III angina. Seven patients had New York Heart Association class III or IV, and 7 patients had class I or II congestive heart failure. Mean left ventricular ejection fraction was $26 \pm 13\%$

In the SB-PTCA group, 1 patient had class III and 12 class IV angina (p = NS). Five patients had class III or IV, and 8 had class I or II congestive heart failure (p = NS). Mean ejection fraction of the SB-PTCA group was $26 \pm 9\% \ (p = NS).$

In the S-PTCA group, 2 patients had left main coronary artery stenosis, seven 3-vessel disease, four 2-vessel disease and one 1-vessel disease. Of the SB-PTCA group, 1 patient had left main stenosis, seven 3-vessel disease and five 2-vessel disease (p = NS).

The preangioplasty percent luminal diameter stenosis was similar in both groups (S-PTCA 93 \pm 3% vs SB- $PTCA 92 \pm 4\%$, p = NS). Results after angioplasty were similar (25 \pm 15% vs 24 \pm 8%, respectively).

In 14 patients undergoing S-PTCA, cardiopulmonary bypass support was inserted by cutdown in 10 and percutaneously in 4. Mean flow rate was 4.5 liters/min and mean duration was 49 minutes. Ten patients had angioplasty by way of the femoral artery and 4 by way of the brachial artery.

In the S-PTCA group, 18 arteries were attempted (1.3 arteries per patient), with 16 vessels successfully dilated. Thirteen of the 14 patients had their target arteries successfully dilated. There were 2 deaths: 1 due to superior mesenteric artery thrombosis, and the other death occurred after dilation of an unprotected left main coronary artery in a patient with a history of bypass surgery. Dissection and thrombus occurred after dilatation and a satisfactory result could not be obtained. Coronary bypass was performed but she died perioperatively due to uncontrollable bleeding.

Of the other 12 S-PTCA patients, 1 patient had gastrointestinal bleeding and was treated with antacids and histamine blockers. One patient required reexploration of the cannula insertion site for bleeding. Eight patients required transfusions. One patient developed acute closure of a nontarget vessel 36 hours after the procedure and had a successful emergency redilatation.

In the 13 SB-PTCA patients, 13 vessels were attempted, all successfully. No patient developed vascular problems or required transfusion. No patient required insertion of percutaneous cardiopulmonary bypass because of hemodynamic collapse or acute closure during the procedure. One patient died suddenly several days after successful PTCA when he suddenly developed chest pain, electrocardiographic changes and rapid hemodynamic deterioration, presumably due to late acute closure of the dilated vessel.

The amount of jeopardized myocardium and left ventricular function before PTCA appear to be strong indicators of PTCA risk. Hartzler et al9 reported a 2.6% procedural mortality in a group of patients with large amounts of jeopardized myocardium.9 Other data suggest that there is 2.7% procedural mortality in patients with left ventricular ejection fraction <40%.2

Patients considered at high risk for PTCA are ofter treated with prophylactic insertion of an intraaortic balloon pump.8 Others have explored the use of coronary sinus retroperfusion,4 and the anterograde perfusion of blood, 5,6 drugs or oxygenated fluorocarbons via the dilatation catheter. Many of these methods have the disadvantage that the dilatation catheter must be passed across the lesion for therapy or sufficient systemic pressure must be present to provide coronary perfusion.

We report a group of high-risk patients undergoing PTCA in whom the angioplasty was performed under the cover of percutaneous cardiopulmonary bypass (supported angioplasty). When it became apparent that there was a high incidence of vascular complications, and we were able to deploy percutaneous cardiopulmonary support rapidly, we began to perform SB-PTCA.

The use of partial cardiopulmonary bypass support during angioplasty appears to be very effective in supporting the systemic circulation. Segmental myocardial function, however, may not be spared and left ventricular segments supplied by target vessels may become abnormal during balloon inflation.

As demonstrated by this study, it appears that S-PTCA is feasible when performed by interventionalists familiar with the percutaneously inserted cardiopulmonary support device. Data from the supported angioplasty registry have defined success and complication rates in a larger group of patients. 10

The present study demonstrates that the initial indications for S-PTCA (i.e., left ventricular ejection fraction ≤25%, or target vessels supplying >50% of the myocardium) are too liberal. Despite the similar precarious coronary anatomy and poor left ventricular function of the SB-PTCA cohort, no patient required percutaneous cardiopulmonary bypass during the procedure. High-risk patients can be managed with SB-PTCA; thus, it is the preferred approach for most patients.

The lack of randomization of these patients weakens this study; however, randomization in the face of such high incidence of vascular problems may no longer be justified, since these patients did well without any systemic support.

We conclude that active S-PTCA should be reserved for patients who have sustained prior hemodynamic collapse during an invasive procedure, or in whom PTCA is aimed at the only patent vessel, or in patients who have exceedingly low left ventricular ejection fraction (<15%).

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Prognosis of Congestive Heart Failure in Elderly Patients with Normal Versus Abnormal Left Ventricular Systolic Function Associated with **Coronary Artery Disease**

Wilbert S. Aronow, MD, Chul Ahn, PhD, and Itzhak Kronzon, MD

he Framingham study demonstrated that the 5-year mortality after the onset of symptoms of congestive heart failure (CHF) was 62% for men and 42% for women. 1 Franciosa et al² found that the 3-year mortality rate for men with chronic CHF due to coronary artery disease or idiopathic dilated cardiomyopathy was 76%. CHF may occur with normal or abnormal left ventricular (LV) ejection fraction.3-8 We report the results from a prospective study of elderly patients with CHF associated with coronary artery disease correlating normal and abnormal LV ejection fraction with cardiac mortality and total mortality.

In a prospective study, CHF was diagnosed in 294 of 1,319 elderly patients (22%) in a long-term health care facility. CHF was diagnosed if 2 criteria were satisfied: (1) Pulmonary basilar rales were heard by 2 physicians including the senior author; and (2) pulmonary vascular congestion was present on the chest roentgenogram interpreted by both an experienced radiologist and the senior author.

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M-mode and 2-dimensional echocardiograms and continuous-wave and pulsed-Doppler echocardiograms were recorded as previously described9-11 at the time CHF was diagnosed. Technically adequate 2-dimensional echocardiograms for measuring LV ejection fraction were obtained in 247 of 294 patients (84%). All echocardiograms were interpreted by an experienced echocardiographer (I.K.). LV volumes at end-diastole and end-systole were calculated by planimetry from the 2-dimensional study. LV ejection fraction was calculat-

TABLE I Baseline Characteristics of Patients with Congestive Heart Failure Associated with Coronary Artery Disease and Normal and Abnormal Left Ventricular Ejection Fraction

Variable	Normal LV Ejection Fraction (n = 68)	Abnormal LV Ejection Fraction (n = 98)	p Value
LV ejection fraction (%) Age (yr) Gender (female) (%) Atrial fibrillation (%) Third heart sound (%) Systemic hypertension (%) Follow-up (mos)	60±6(51-80) 84±6(62-96) 53(78) 23(34) 25(37) 36(53) 23±17(1-58)	34 ± 9 (12-49) 81 ± 8 (62-97) 63 (64) 36 (37) 88 (90) 58 (59) 16 ± 13 (2-53)	<0.001 <0.05 NS NS <0.001 NS
LV = left ventricular; NS = no	ot significant.		

TABLE II Incidences of Cardiac Death and Total Death in Patients with Congestive Heart Failure Associated with Coronary Artery Disease and Normal and Abnormal Left Ventricular Ejection Fraction

	Normal LV Ejection Fraction (n = 68)		Abnor Ejection Fraction (n = 9		
	No	(%)	No.	(%)	p Value
Cardiac death	35	(51)	83	(85)	<0.001
Noncardiac death	3	(4)	0	(0)	< 0.05
Total death	38	(56)	83	(85)	< 0.001

ed as: (LV end-diastolic volume — LV end-systolic volume)/LV end-diastolic volume × 100%. CHF with abnormal systolic function was diagnosed if the LV ejection fraction was <50%. 12 CHF with normal systolic function was diagnosed if the LV ejection fraction was ≥50%.

Patients were considered at entry into the study to have coronary artery disease if they had a documented clinical history of myocardial infarction, electrocardiographic evidence of Q-wave myocardial infarction or angina pectoris. A systolic blood pressure ≥160 mm Hg on 3 occasions was considered systolic hypertension. A diastolic blood pressure ≥90 mm Hg on 3 occasions was diastolic hypertension. Aortic or mitral valvular heart disease was diagnosed by continuous-wave and pulsed Doppler echocardiography as previously described. Mean age of the 166 patients with CHF associated with coronary artery disease was 82 ± 7 years (range 62 to 97)

Patients were followed for incidences of cardiac death and total death. Follow-up was from the time LV ejection fraction was obtained until the time of death or cutoff date for analysis of the data. Group comparisons were made using the t test for independent means and chi-square analysis. Survival curves of patients with normal and abnormal LV ejection fraction were estimated using the Kaplan-Meier product limit estimator and tested for homogeneity with the log-rank and Wilcoxon tests. The relation between prognostic or explanatory variables measured at baseline and time to death was analyzed in the 166 patients with CHF and coronary artery disease using the stepwise procedure based on the Cox regression model (known as proportional-hazards model) to determine which combination of prognostic variables was most suitable for predicting patient surviv-

Normal LV ejection fraction occurred in 116 of 247 patients (47%) with CHF and in 68 of 166 patients (41%) with CHF and coronary artery disease. Table I lists the baseline characteristics of patients with CHF and coronary artery disease with normal and abnormal LV ejection fraction and levels of statistical significance. Table II lists the incidences of cardiac death and total death in patients with CHF and coronary artery disease with normal and abnormal LV ejection fraction and levels of statistical significance.

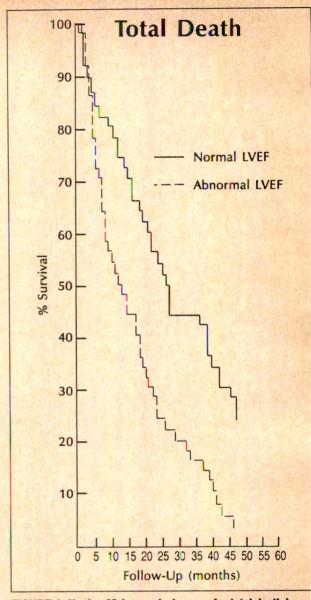


FIGURE 1. Kapian-Meier survival curves for total death in patients with congestive heart failure associated with coronary artery disease and normal left ventricular ejection fraction (LVEF) and abnormal LVEF.

Kaplan-Meier survival curves for total death are il lustrated in Figure 1. Both the log-rank and Wilcoxon tests show that the 2 survival curves are significantly different (p <0.001).

With use of a stepwise proportional-hazards model patients with abnormal LV ejection fraction have 2.30 times higher mortality rates than patients with normal LV ejection fraction after controlling other prognostivariables. Patients with hypertension have 1.40 time higher death rates than those without hypertension after controlling other prognostic variables. There was a 1.2-times higher mortality rate for an increment of 10 year of age after controlling other prognostic variables.

The prevalence of normal systolic function in our prospective study of elderly patients with CHF associate with coronary artery disease was 41%. The prevalence of normal systolic function in patients with CHF in other

studies was reported as 40%,³ 36%,⁴ 42%,⁵ 34%,⁶ 41%⁷ and 13%.⁸ A third heart sound heard by 2 physicians was present in 37% of our patients with CHF and normal systolic function. The prevalence of an audible third heart sound in patients with CHF and normal systolic function was reported in other studies as 45%,³ 41%⁴ and 21%.⁶

Echocardiography, especially when combined with Doppler studies, is important in the management of patients with CHF. 3.6,13 Determination of LV systolic function and causative mechanisms of CHF is important in determining long-term therapy of CHF. In our population of 247 patients with CHF, valvular heart surgery was recommended to patients with CHF on the basis of Doppler echocardiographic studies. Digitalis was not administered to patients with normal systolic function unless atrial fibrillation was present. Vasodilators were administered to patients with abnormal systolic function unless severe or moderate aortic stenosis was present, and to patients with normal systolic function only if needed in addition to diuretics to treat hypertension.

Data from our prospective study showed that LV ejection fraction was the most important prognostic variable for mortality in elderly patients with CHF associated with coronary artery disease. Survival rates for patients with CHF associated with coronary artery disease and normal LV ejection fraction were 78% at 1 year, 62% at 2 years, 54% at 3 years and 44% at 4 years. Survival rates for patients with CHF associated with coronary artery disease and abnormal LV ejection fraction were 53% at 1 year, 29% at 2 years, 22% at 3 years and 15% at 4 years. Cohn and Johnson⁸ observed that the average annual mortality in the Vasodilator Heart Failure Trial was 8% for patients with CHF and a normal LV ejection fraction and 19% for patients with CHF and an abnormal LV ejection fraction.

In addition to LV ejection fraction, hypertension and age were independent variables that predicted death in

our patients with CHF associated with coronary artery disease. Patients with abnormal LV ejection fraction had a similar prevalence of hypertension as patients with normal LV ejection fraction. Patients with CHF and normal LV ejection fraction were older than patients with CHF and abnormal LV ejection fraction.

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Delayed Coronary Angioplasty After Thrombolytic Therapy for Acute Myocardial Infarction

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The role for and timing of percutaneous transluminal coronary angioplasty (PTCA) after thrombolytic therapy for acute myocardial infarction (AMI) remains controversial. Three large randomized trials¹⁻³ have demonstrated no benefit from PTCA performed within 48 hours of thrombolysis. Delayed PTCA performed after 48 hours has not been as carefully studied. Some advocate its use only for patients with evidence of recurrent ischemia.³ In patients with unstable angina and angiographically

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evident intracoronary thrombus, delaying PTCA until after a course of anticoagulation and antiplatelet therapy has improved PTCA success and reduced thromboembolic coronary occlusion. Whether delaying PTCA after thrombolysis for AMI produces similar benefits is unknown. We report our experience with delayed PTCA performed after thrombolysis for AMI.

Between November 1986 and July 1989, 3,256 patients were entered in a PTCA database. Of these, 151 consecutive patients who underwent PTCA of the infarct-related artery 3 to 14 days (mean 6) after thrombolysis for AMI were identified. The indication for PTCA was determined by each patient's private cardiologist. Only stenoses with >70% diameter narrowing were

TABLE I Distribution of Coronary Stenoses and Angioplasty Success

Infarct-Related			
Arteries	n (%)	Success (%)	
LAD	55 (36)	49 (89)	
LC	26 (17)	21 (81)	
Right	66 (44)	59 (89)	
SVG	4(3)	4 (100)	
Total	151 (100)	133 (88)	

LAD = left anterior descending; LC = circumflex; Right = right coronary artery; SVG = saphenous vein graft.

considered for PTCA. PTCA was performed using standard techniques. Aspirin and heparin were routinely administered before PTCA. Aspirin, heparin and a calcium channel blocker were routinely given after angioplasty.

PTCA was considered successful if the lesion was reduced to <50% diameter narrowing without a major complication (acute vessel closure, emergency bypass surgery, AMI, death). Hospital survival was determined by a review of medical records.

Among the 151 patients, 116 (77%) were men (aged 35 to 80 years [mean 57]). A similar number of patients had received streptokinase (48%) and tissue plasminogen activator (52%).

Overall, left ventricular ejection fraction was normal (>50%) in 19 (13%), mildly impaired (40 to 50%) in 94 (62%), moderately impaired (30 to 40%) in 26 (17%) and severely depressed (<30%) in 12 (8%). Sixty-nine patients (46%) had 1-vessel coronary disease, 68 (45%) had 2-vessel disease and 14 (9%) had 3-vessel disease. PTCA of only the "infarct-related" stenosis was performed in 106 (70%) patients. Multivessel PTCA was performed in 16 (11%) and multilesion PTCA in the remaining 29 (19%)

The results of PTCA are listed in Table I. Right coronary and left anterior descending artery dilatations were the procedures most frequently attempted. Successful dilatation was achieved in 133 of the 151 lesions (88%). Half of the unsuccessful attempts (9 of 18) occurred in the 23 patients with total coronary occlusions. The outcome of PTCA was similar for patients treated with streptokinase and tissue plasminogen activator. Serious complications were encountered in 9 patients (6%). Acute vessel closure occurred in 5 patients (3%) requiring repeat PTCA in 3 and emergency bypass surgery in 2 other patients. Emergency coronary bypass surgery was performed in 3 other patients owing to intracoronary thrombus formation without evidence of ischemia. There was 1 myocardial infarction and 1 (0.7%) patient died in the hospital after bypass surgery.

This retrospective study of delayed angioplasty after thrombolysis for AMI demonstrates an 88% complication-free success rate. This is comparable to the results generally achieved by elective PTCA. The results are also similar to the 94 and 84% success rates of delayed PTCA achieved in 2 small randomized trials. 1,5 The 3% emergency bypass rate in the present study is identical to that reported in these trials. The observed 6% overall complication rate compares favorably to the reported 20% occurrence of reinfarction and ischemia after thrombolytic therapy without subsequent PTCA.2,5 When acute vessel closure does occur during delayed PTCA, it can be managed immediately by interventional techniques and bypass surgery. Alternatively, untimely reinfarction after thrombolysis may produce a longer delay before interventional procedures are instituted and restoration of perfusion achieved.

Although early PTCA after thrombolysis has not been supported by randomized trials, 1-3 emerging evidence suggests potential benefits from delayed PTCA. After successful thrombolysis, PTCA is necessary to improve exercise ejection fraction.6 Unsuccessful thrombolysis with persistent vessel occlusion after AMI is associated with a higher long-term mortality and lower left ventricular ejection fraction than if coronary patency is achieved even late after the acute period of infarction.6,7 Although PTCA success for total occlusions was only 61% during this series, recent technical improvements have increased our success rate to 94% for recent occlusions.8

Unlike reported results of early PTCA after thrombolysis, delayed PTCA was found to be safe and effective in this study. These results are subject to the limitations of a retrospective study and the potential for bias in patient referral and case selection at a tertiary care center. Prospective evaluation of delayed PTCA will be required to confirm these results and evaluate the effects of anticoagulation and other factors on outcome.

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Natural History of Posterobasal Left Ventricular Aneurysm

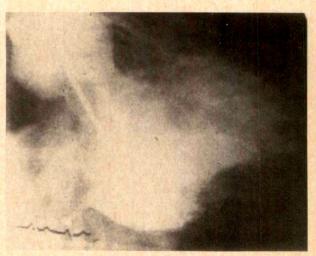
Morteza Amidi, MD, Steven Royal, MD, Edward Curtiss, MD, and Maureen Puskar, RN

he data from 2,500 patients undergoing cardiac catheterization were reviewed to detect the presence of a posterobasal left ventricular (LV) aneurysm. An aneurysm was defined as a localized mural protrusion that extended beyond the LV contour during both systole and diastole.1,2 In all cases, left ventriculography was performed in the 30 degree right anterior oblique position. The area over the left ventricle exclusively at the aneurysm and the area of the aneurysm were determined planimetrically (Figure 1). The ratio of aneurysm area to total LV area was used as an index of aneurysm size; it was estimated for both systole and diastole. The length of the longitudinal chord at the connection of the aneurysm to the left ventricle was compared with the largest similar cord of the aneurysm, per se. The smallest LV size was considered systole and the largest LV area usually simultaneous with the peak of the R wave on the electrocardiogram over the cine trace was considered diastolic LV area.

Fourteen patients (0.6%) were identified as having a posterobasal LV aneurysm. All patients had a history of myocardial infarction. The infarction occurred 1.5 to 15 years before our study. No patient had symptomatic congestive heart failure or history of sudden collapse suggestive of rhythm disturbances. All 14 patients had electrocardiographic evidence of diaphragmatic wall myocardial infarction; all had a large O wave ≥0.04 second and depth of >3 mV in lead III. ST elevation ≥0.1 mm was present in leads II, III and aVF only in 1 patient. One patient had left anterior fascicular block, and I had anomalous atrioventricular excitation of the Wolff-Parkinson-White type. In all patients, the mouth of the aneurysm to the left ventricle was the largest longitudinal dimension of the former consistent with the true aneurysm. The area of aneurysm ranged from 9 to 42% of the LV area in diastole and 8 to 50% in systole. During systole the aneurysmal area increased in 3, remained unchanged in 4 and decreased in 7 patients. No aneurysm with circumscribed neck suggestive of false aneurysm was observed among these patients. The patients underwent cardiac catheterization during the last 6 years and diaphragmatic wall infarction ranged from 18 months to 15 years. Two patients died from noncardiac causes (1 from carcinoma of the stomach and the other from pneumonia and sepsis). Four patients underwent coronary artery bypass grafting for symptoms related to additional coronary artery disease. Only 1 patient had ventricular dysrhythmia that required electrophysiologic study. Operative intervention was successful but aneurysmectomy was not performed. Four patients continued to have stable angina.

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Decision-making for management of posterobasal LV aneurysm is difficult because of lack of reported followup data. Buehler et al3 described 6 cases of false aneurysm among 10 posterobasal LV aneurysms, and concluded that most aneurysms in this location are false, that they have high propensity for rupture, and that operation is recommended. Codini et al4 found 20 cases of posterobasal LV aneurysm among 354 operations for LV aneurysm during a 10-year period. Only 1 case of false aneurysm was present among these cases. These reports originated in referral surgical centers and therefore these cases are highly selective. Experience with our 14 cases of LV aneurysm of various sizes indicates the following characteristics: (1) Angiography was in keeping with the true aneurysm of the diaphragmatic wall in all patients. (2) Clinical progression of these patients were very satisfactory. (3) No cardiac rupture or peripheral emboliza-



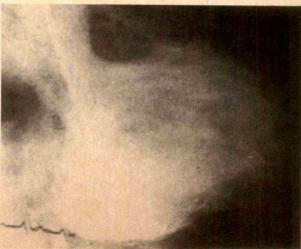


FIGURE 1. Left ventricular angiogram in systole and diastole showing posterobasal aneurysm.

tion originated from the left ventricle where noted. (4) No LV aneurysmectomy was necessary in any patient.

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Physician Attitudes Toward the Use of Type IC Antiarrhythmics After the Cardiac Arrhythmia Suppression Trial (CAST)

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n the mid 1980s, 2 compounds considered to be class IC1 antiarrhythmic agents, flecainide and encainide, received approval in the U.S. for treating symptomatic, or life-threatening ventricular arrhythmias, or both. Despite a notable proarrhythmia risk, 1-12 their use grew because of high efficacy, low organ toxicity, and otherwise excellent patient tolerance. In August 1989, however, the Cardiac Arrhythmia Suppression Trial (CAST)13,14 highlighted the proarrhythmic risk of these 2 agents and the Food and Drug Administration (FDA) responded by relabeling these drugs. They are now approved in the U.S. only for the treatment of lethal ventricular tachyarrhythmias. FDA sanctions and specific package labeling, however, have never guaranteed that a drug will be used according to such sanctions and instructions. Physicians are free to exercise therapeutic judgment, assuming an appropriate rationale and support from the medical literature. Given the favorable efficacy, convenience and side effect profiles of encainide and flecainide apparent before CAST, we hypothesized that their use might continue despite the recent FDA guidelines. To test this belief, we formulated a questionnaire concerning the use of class IC agents after CAST. We assumed this information would interest drug regulators, pharmaceutical manufacturers, investigators and those physicians in practice who prescribe or avoid IC agents without certainty as to peer behavior.

The questionnaire, reproduced in Table I, was sent to all U.S. and Canadian physicians in the North American Society of Pacing and Electrophysiology (NASPE) as well as to a small random sample of NASPE physicians not from North America. This constituted approximately 950 physicians. The survey, however, was not developed by NASPE, and the results do not imply any NASPE position or sanction. NASPE physicians were targeted to receive the questionnaire because we felt they had a strong interest in patients with arrhythmias, had the most experience among their peers with antiarrhythmic therapy, and may constitute the most suitable model for other physicians using antiarrhythmic drugs to consider, Also, as leaders in the use of antiarrhythmic thera-

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py, these physicians may represent a reasonable microcosm for the FDA and pharmaceutical manufacturers to view. The responses were anonymous. The 374 questionnaires returned by April 1, 1990, form the basis of this report (Table II).

The use of class IC agents before CAST was assessed with question 7, to which 166 (45%) of those responding indicated that their use was mostly for ventricular ar-

TABLE I Questionnaire

Please put a check mark next to each applicable answer.

- 1. Has your use of class IC agents (encainide, flecainide)
 - a) increased
 - b) decreased
 - c) remained the same

since the publication of the CAST results?

- 2. Do you/would you still use encainide and/or flecainide?
 - a) yes
 - b) no
- 3. If you currently use IC drugs, do you/would you limit them to patients with sustained ventricular tachyarrhythmias?
 - a) yes
 - b) no
- If you currently use IC agents for arrhythmias other than sustained ventricular tachyarrhythmias, do you/would you use them:
 - a) for nonsustained ventricular tachycardia
 - b) for supraventricular tachyarrhythmias
 - c) for symptomatic premature complexes
 - d) for arrhythmias associated with preexcitation
 - e) others (please specify)
- 5. If you currently use IC agents for sustained ventricular tachyarrhythmias, do you/would you ever use them as the first drug?
 - a) yes
 - b) no
- 6. In about how many patients taking encainide or flecainide did you stop drug therapy because of the CAST results?
 - a) 100%
 - b) >50%
 - c) 25-50%
 - d) <25%
- In what types of patients was your use of IC agents most frequent prior to CAST?
 - a) ventricular arrhythmias
 - b) supraventricular arrhythmias
- 8. In what types of patients did you stop IC drug therapy after CAST?
- 9. If a new IC agent became available, would your use of it
 - a) be the same as encainide and flecainide?
 - b) depend upon the package labeling?

CAST = Cardiac Arrhythmia Suppression Trial.

rhythmias; 185 (50%) indicated use mostly for supraventricular arrhythmias; and 19 (5%) indicated use about equal for both ventricular and supraventricular arrhythmias. Thus, before CAST, about half of the respondents used encainide and flecainide predominately

for unapproved indications.

The frequency of IC use subsequent to CAST was assessed with question 1, to which 295 (79%) of those responding indicated that their use had decreased, whereas 77 (21%) indicated that their use was unchanged. Two respondents reported a surprising increase. Additionally, the percentage of patients in which encainide and flecainide were stopped because of CAST or FDA relabeling was assessed with question 6, to which 21 (6%) of those responding said 100%, 102 (27%) said >50 but <100%, 58 (16%) said 25 to 50%, 126 (34%) said <25%, whereas 66 (18%) indicated no discontinuation. Thus, most respondents decreased their use of encainide and flecainide after CAST (question 1) but were not dissuaded from continuing them in the majority of patients already on drug therapy. Moreover, 339 (91%) of those responding to question 2 said they still use encainide or flecainide, whereas only 35 (9%) said they do not. This suggests that although the use of encainide and flecainide has diminished, only 7% (21/308) of those who decreased their use have actually stopped using these agents, with more stopping them in patients previously started (question 6) than indicating that they would no longer begin them (question 2).

The pattern of IC use subsequent to CAST was assessed with questions 3 and 4. Only 69 (18%) of those responding to question 3 indicated that use after CAST was limited to sustained ventricular tachyarrhythmias, whereas (question 4) 101 indicated use for nonsustained ventricular tachycardia, 89 for symptomatic premature complexes, and 304 for supraventricular tachyarrhythmias. Most physicians indicated more than 1 choice for question 4. Additionally, when respondents were asked (question 5) whether they ever use class IC agents as initial antiarrhythmic therapy when treating sustained ventricular tachyarrhythmias, 322 (90%) of those responding said "no" whereas an unexpected 36 (10%)

said "yes."

The potential response to new class IC agents such as propafenone, 15 if and when available, was assessed with question 9, to which 168 (45%) of those responding indicated use identical to encainide and flecainide (perhaps viewing all class IC agents as the same), whereas 129 (35%) indicated use dependent upon specific package labeling, 61 (16%) amended the questionnaire to indicate use dependent upon the specific drug and its medical literature (in contrast to product labeling alone), and 29 had miscellaneous additional comments.

Finally, to assess internal consistency of answers as well as to acquire more details on specific types of patients in whom class IC agents are now being used, question 8 asked (in free text form) the type of patients in whom physicians did not discontinue encainide or flecainide after CAST. Encainide and flecainide were continued by 208 respondents for supraventricular tachyarrhythmias (with 49 specifically denoting patients with preexcitation), by 102 for sustained ventricular tachy-

TABLE II Resonses to Each Item in Table I No. of Question Item Responses A B 295 C 77 2 A 339 B 35 A 69 B 305 A 101 В 304 C 89 D 266 E 5 36 В 322 A 21 В 102 C 58 D 126 E 66 A 204 В 185 See text 168 129

Responder write-ins = 77 (see text).

cardia or fibrillation, and by 37 for nonsustained ventricular tachycardia, or symptomatic premature complexes, or both. Thus, the majority of patients who were continued on a type IC agent remained on that agent for supraventricular tachyarrhythmias. Judging from the responses to question 4, this is also the major reason for starting a class IC agent at present. In contrast, responses to question 8 suggest that very few patients with nonsustained ventricular tachycardia, or premature complexes, or both, were continued on the drugs after CAST and FDA relabeling, whereas responses to question 4 indicate a willingness to use them now for such patients in a greater proportion, as compared to supraventricular tachyarrhythmia patients, than was the case immediately after CAST. Additional comments made in response to question 8 included use only with guidance by electrophysiologic testing (48 respondents), use when patients are refractory to or intolerant of other agents (52 respondents), continued use when patients were clinically stable on an IC drug at the time of CAST (28 respondents), insistence on normal ventricular function or absence of coronary artery disease, or both (91 respondents), and drug stopped at the patient's request because of media reports (7 respondents).

Because physicians are not required to use drugs for the indication(s) approved by the FDA, a drug's use may differ from that which is specified in the package labeling. Accordingly, when the labeling for encainide and flecainide was changed after CAST, we were uncertain as to how their actual use would be affected. The wide publicity of the CAST results in the lay press, the rapid and direct notification of physicians of these results, the abrupt freeze on encainide and flecainide research by the manufacturers and the discontinuation of their advertising presumably should have led to a marked decline in the

use of these agents and contraction of their use to patients with the new restricted indications. However, physician experience and satisfaction with these drugs might favor their continued use. Also, the limited patient population enrolled in CAST with uncertain extrapolation to other patients, serious design concerns about CAST, which became particularly evident in retrospect, results of class IC use in numerous other published studies, as well as other factors, might mitigate against the marked restriction in the use of encainide and flecainide recommended by the FDA and envisioned by their manufacturers. As a preliminary effort to assess the use of IC agents after CAST, we formulated our questionnaire. It was sent to members of NASPE who, by their membership, comprise a group of physicians particularly interested and experienced in the treatment of cardiac rhythm disorders. We have no data to indicate how the use of drugs by such experts may differ from that of other physicians, though it is our bias that use by non-arrhythmologists may initially be more conservative than but later follow the trend set by their more expert colleagues. Additionally, while we received back only about 40% of the questionnaires mailed, it was our a priori assumption that those NASPE physicians who are primarily surgeons and whose arrhythmia management is essentially limited to device (pacemaker, defibrillator) implantation would not respond. Thus, the receipt of 374 questionnaires probably constitutes a response by the majority of the physicians we hoped to target, though this assumption may be incorrect. Whether those who did not respond would have answered similarly to or differently from our respondents is unknown. However, even if all of the non-responders said they no longer use IC agents, the overall incidence of use in all physicians surveyed would still approach 32%-1 out of every 3 physicians!

Our pilot survey indicates that although approximately 80% of respondents decreased the use of IC agents after CAST: (1) about 80% continued encainide and flecainide in most of the patients already on therapy before CAST; (2) about 90% will still begin these agents; and (3) a substantial percentage of respondents used encainide and flecainide for unapproved indications before CAST and continue to do so now, with more using them for supraventricular tachyarrhythmias than for any other arrhythmia. Only 20% limit use to sustained ventricular tachyarrhythmias, despite the relabeling. It would also appear, however, that a healthy concern about their use in patients with organic heart disease or without electrophysiologic guidance (at least in patients with ventricular arrhythmias) is beginning to take hold. These patterns indicate that FDA instructions cannot be equated with actual patterns of physician usage of available pharmaceuticals. Further details about IC usage patterns would be of great interest and we would encourage a larger, more thorough

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Treatment of Ventricular Arrhythmias in Children Without Structural Heart Disease With Class IC Agents as Guided by Invasive Electrophysiology

Christopher L. Case, MD, and Paul C. Gillette, MD

lthough the efficacy of class IC antiarrhythmic agents A in the treatment of supraventricular and ventricular arrhythmias in adults has been clearly demonstrated, serious proarrhythmic effects have been reported.1 These agents have also proven useful in the pediatric population, but there is growing concern that similar proarrhythmic potential exists. 2,3 Recognizing that these drugs, although very useful, may also be deadly, we have adopted a protocol at the Medical University of South Carolina that uses invasive ventricular stimulation after drug administration to help assess the risk/benefit ratio of these agents in the treatment of ventricular arrhythmias. Since mid-1987, all 23 children with ventricular arrhythmias treated with IC agents have had invasive stimulation performed after drug administration to evaluate efficacy or proarrhythmia, or both. Ten of these children with structurally normal hearts, treated solely with IC agents, were tested in the electrophysiology laboratory both before and after drug administration; data from these 10 patients were used in this investigation (Table I).

Five boys and 5 girls (median age 8 years) comprised the study patients. Eight were treated with flecainide and 2 with encainide. All children were begun on IC agents in the hospital while being monitored on telemetry. The starting dose of flecainide was 70 to 100 mg/m²/day, given every 12 hours, with incremental increases until therapeutic response was attained. The average flecainide dose of the study group was 106 ± 49 mg/m². Encainide was started at 30 to 60 mg/m²/day, given every

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8 hours, with a similar gradual increase until efficacy was reached. The average encainide dose was 100 ± 35 mg/m2. A therapeutic response was judged to be present if sustained ventricular tachycardia was abolished or premature ventricular contractions reduced to <10/hour as evaluated by Holter monitoring, or both. After clinical efficacy was established, all patients underwent programmed ventricular stimulation in the electrophysiology laboratory. The protocol included the delivery of single and double ventricular extrastimuli into sinus rhythm or a ventricular paced rhythm. Eight-beat ventricular burst pacing was performed until 2:1 noncapture was reached. Proarrhythmia was defined as a ventricular arrhythmia induced in the study after IC therapy. which had a shorter cycle length, was more sustained, was hemodynamically less stable, or was more easily induced than in the study before IC therapy.

Of the 10 patients studied, 1 satisfied criteria for proarrhythmia. This was an 8-year-old girl (patient no. 6) with prolonged QT syndrome who had ventricular tachycardia induced in her study after IC therapy, which was both faster and more disorganized than that induced before IC therapy. This child's clinical tachycardia had previously been unsuccessfully controlled with propranolol and mexilitine, individually and in combination. She was cautiously started on flecainide and had her electrophysiologic evaluation performed while on a dose of 75 mg/m2. The proarrhythmic effect was induced with burst ventricular pacing, and the patient had no sequelae from this episode. Examination of the electrocardiograms before and after IC therapy of all study patients revealed that both flecainide and encainide had a tendency to lengthen the PR, QRS and QTc intervals. The degree of lengthening of the electrocardiographic inter-

Pt.	Age (yr) & Sex	Clinical Arrhythmia	VT Induced Before IC Therapy	IC Therapy	VT Induced After IC Therapy EPS
1	2F	VT	+	Encainide	0
2	2F	VT	+	Flecainide	0
3	5 F	VT	+	Flecainide	0
4	5 M	VT	+ *************************************	Flecainide	0
5	8F	VT	+	Flecainide	0
6	8F	VT	+	Flecainide	+
7	13 M	VT (NS)	+ (NS)	Flecainide	0
8	15 M	VT (NS)	+ (NS)	Flecainide	0
9	16 M	AF (NS) VT (NS)	+ (NS)	Flecainide	Ö
10	18 M	VT (NS)	+ (NS)	Encainide	0

vals after IC therapy in the child with inducible proarrhythmia was not excessive when compared to the study group as a whole. Likewise, the drug dose of this child was lower than the average flecainide dose of the study group.

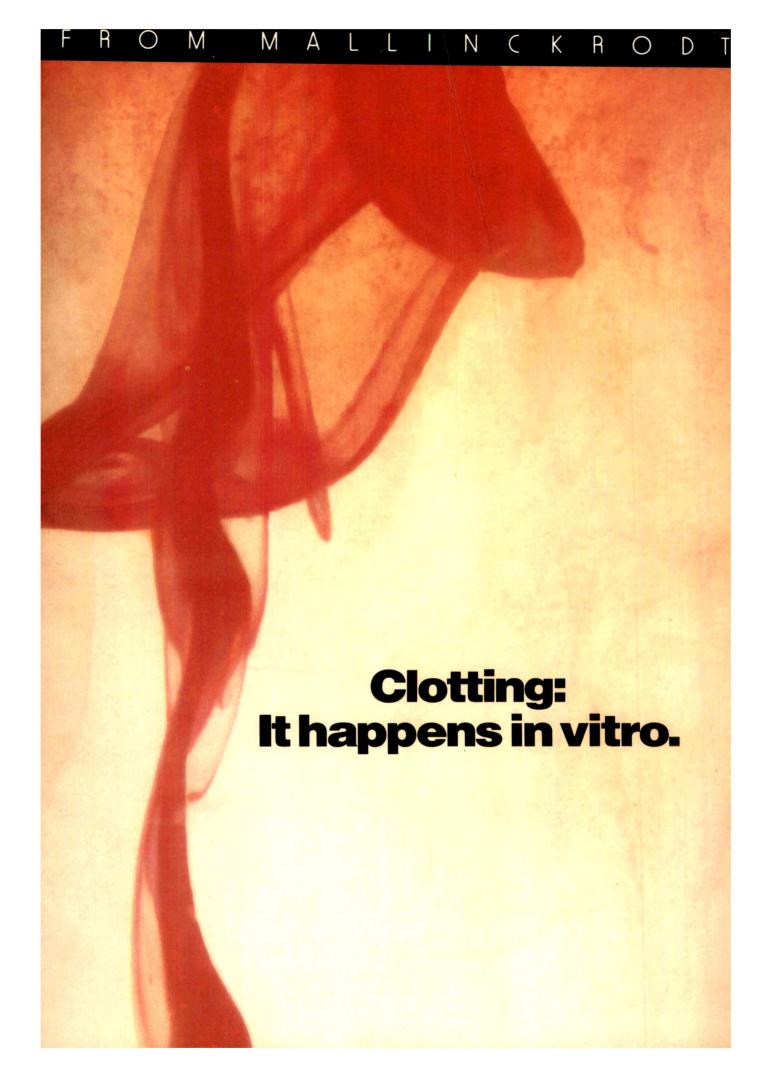
All 10 patients were alive and well with ≥1 year of follow-up. The patients who were noninducible on IC agents have continued their IC medications with good efficacy and no suspected clinical proarrhythmia. The 1 patient with inducible proarrhythmia has since had a stellate ganglionectomy, but still needs mexilitine to control her arrhythmia.

Although the recent findings of the Cardiac Arrhythmic Suppression Trial have highlighted the potential proarrhythmic effects of IC agents,4 the implications of these findings for the pediatric patient are uncertain. In an attempt to avoid total abandonment of the use of IC agents in children, we elected to use invasive ventricular stimulation after IC therapy to help assess the relative risk/benefit ratio of these agents in the control of pediatric ventricular arrhythmias. Since 1987, we have found that 1 of 10 children with structurally normal hearts who

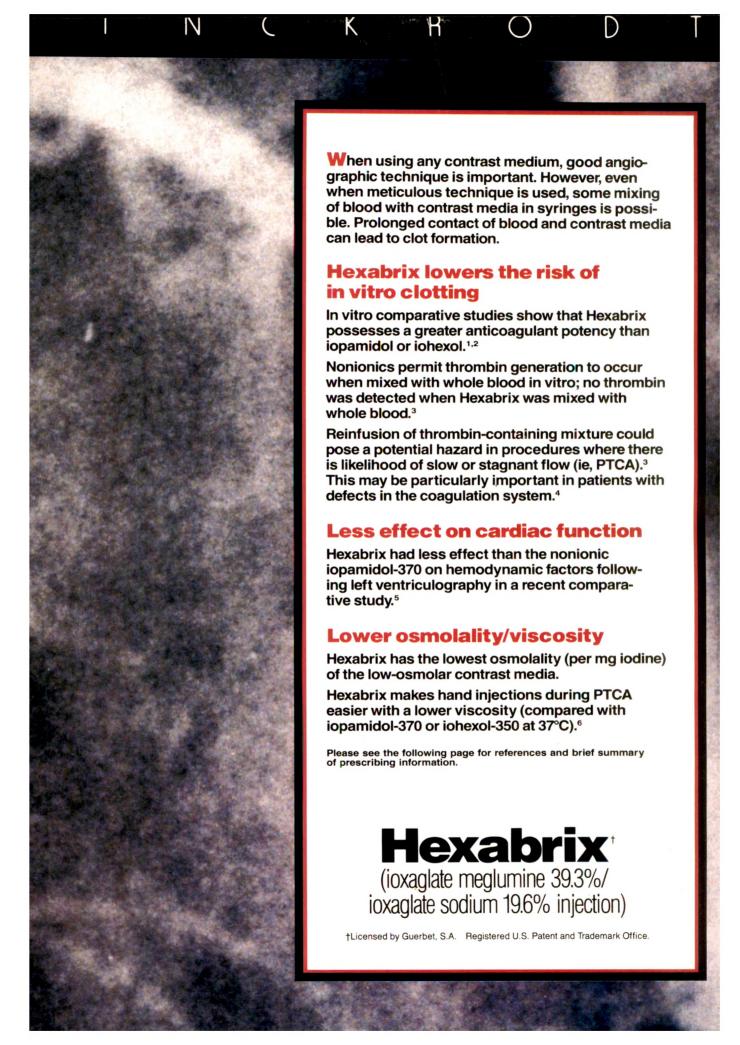
are receiving IC agents have satisfied criteria for proarrhythmia as evaluated by programmed ventricular stimulation. This protocol, which relies on invasive electrophysiology, does have some limitations. It is quite possible that proarrhythmic effects observed during ventricular stimulation may not be clinically relevant. 5,6 Despite this limitation, we have used data obtained from the electrophysiology laboratory as a critical element in the management strategy involving the use of IC agents in the pediatric patient with ventricular arrhythmias.

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CONTRAINDICATIONS

CONTRAINDICATIONS

XABRIX is contraindicated for use in myelography. Refer to ECAUTIONS concerning hyperessitivity. Hysterosalpin-graphy should not be performed during the menstrual inod: in prepanar patents: in patients with known infection any portion of the genital tract; or in patients in whom vical conization or cuertage has been performed within days. Arthrography should not be performed if infectis present in or near the joint.

WARNINGS

ic iodinated contrast media inhibit blood coagulation, in 70, more than nonionic contrast media. Nonetheless, it is udent to avoid prolonged contact of blood with syringes con-

ning ionic contrast media.

Serious, rarely fatal, thromboembolic events causing ocardial infarction and stroke have been reported during Serious, rarely tatal, thromboembolic events causing ocardial infaction and stroke have been reported during giographic procedures with both ionic and nonionic contrast did. Therefore, meticulous intravascular administration hinique is necessary, particularly during angiographic produres, to minimize thromboembolic events. Numerous tors, including length of procedure, catheter and syringe iteral underlying disease state, and concomitant medicans may contribute to the development of thromboembolic ents. For these reasons, meticulous angiographic techques are recommended including close attention to guidere and catheter manipulation, use of manifold systems d/or three-way stopcocks, frequent catheter flushing he hepartnized saline solutions and minimizing the length the procedure. The use of plastic syringes in place of glass ringes has been reported to decrease but not eliminate si likelimod of in vitro clotting. As with any contrast medium, serious neurologic sequelae, sluding permanent paralysis, can occur following cerebral

cluding permanent paralysis, can occur following cerebra: leriography, selective spinal arteriography and arteriography vessels supplying the spinal cord. The injection of a contrast edium should never be made following the administration vasopressors, since they strongly potentiate neuro

vasopressors, since they strongly potentiate neutrojic effects.

In patients with subarachnoid hemorrhage, a rare associanetween contrast administration and clinical deterioration,
cluding convulsions and death, has been reported,
erefore, administration of intravascular indinated contrast
edia in these patients should be undertaken with caution.

A definite risk exists in the use of intravascular contrast
ents in patients who are known to have multiple myelome. In
ch instances anuria has developed, insulting in progressive
emia, renal failure and eventually death. Although neither the
ntrast agent nor dehydration has separately proved to be the
use of anuria in myeloma, it has been speculated that the
mbination of both may be a causative factor. The risk in
yelomatous patients is not a contraindication to the produre, however, partial dehydration in the preparation of
se patients for the examination is not recommended since
s may predispose to precipitation of myeloma protein in s may predispose to precipitation of myeloma protein in a renal tubules. No form of therapy, including dialysis, has en successful in reversing the effect. Myeloma, which curs most commonly in persons over 40, should be con-lered before instituting intravascular administration of

Administration of radiopaque materials to patients known suspected to have pheochromosytoms should be per-rimed with extreme caution. It, in the opinion of the ysician, the possible benefits of such procedures outweigh e considered risks, the procedures may be performed, wever, the amount of radiopaque medium injected should kept to an absolute minimum. The Blood pressure should be sessed throughout the procedure, and measures for treat-ent of a hypertensive crists should be available. Since intravascular administration of contrast media ymote sickling in individuals who are homozygous for sickle il disease, fluid restriction is not advised. Administration of radiopaque materials to patients knowl

Il disease, fluid restriction is not advised. In patients with advanced renal disease, iodinated contrast edia should be used with caution and only when the need for e examination dictates, since excretion of the medium may impaired. Patients with combined renal and hepatic sease, those with severe hypertension or congestive heart ilure and recent renal transplant recipients present an

Renal failure has been reported in patients with live Renal failure has been reported in patients with liver stunction who were given an oral cholecystographic agent lowed by an intravascular iodinated radiopaque agent and so in patients with occult renal disease, notably diabetics and per tensives. In these classes of patients there should be no id restriction and every attempt made to maintain normal dration prior to contrast medium injection, since dehydra-in is the single most important factor influencing further nal imparment.

nal impairment.

Caution should be exercised in performing contrast colum studies in patients with endotoxemia and/or those the elevated body temperatures.

Reports of thyroid storm occurring following the intra-scular use of iodinated radiopaque agents in patients with perthyroidism or with an autonomously functioning thyroid vidule, suggest that this additional risk be evaluated before of this firm, obline-containing contrast apents may affer e of this drug. lodine-containing contrast agents may alter e results of thyroid function tests which depend on iodine timation, e.g., PBI, and may also affect results of radioactive dine uptake studies. Such tests, if indicated, should be perrmed prior to the administration of this preparation

PRECAUTIONS

PRECAUTIONS agnostic procedures which involve the use of iodinated travascular contrast agents should be carried out under the rection of personnel skilled and experienced in the particular ocedure to be performed. All procedures utilizing contrast edia carry a definite risk of producing adverse reactions like most reactions are minor, life-threatening and fatal reactions are more infle-threatening and fatal reactions are more infle-threatening and fatal reactions are union, life-threatening and fatal reactions are union, life-threatening and training adverse reactions of all types should always be available. If a serious reaction should occur, immediately discontinue administration nec severe delayed reactions have been known to occur, nergency facilities and competent personnel should be available for at least 30 to 60 minutes after administration. (See DVERSE REACTIONS.)

Preparatory dehydration is dangerous and may contribute.

Preparatory dehydration is dangerous and may contribute acute renal failure in infants, young children, the elderly,

patients with pre-existing renal insufficiency, patients with multiple myeloma, patients with advanced vascular disease and diabetic patients. Acute renal failure has been reported in diabetic patients

Acute renal failure has been reported in diabetic patients with diabetic nephropathy and in susceptible non-diabetic patients (often elderly with pre-wasting renal disease) following the administration of iodinated contrast agents. Therefore, careful consideration of the potential risks should be given before performing this radiographic procedure in these patients. Severe reactions to contrast media often resemble allergic responses. This has prompted the use of several provocative pretesting methods, one of which can be relied on to predict severe reactions. No conclusive relationship between severe reactions and antigen-antibody reactions or other manifications of allergy has been established. The possibility of an idiosyncratic reaction in patients who have previously received acountrast medium without ill effect should always be considered. Prior to the injection of any contrast medium, the patient should be questioned to obtain a medical history with emphasis on allergy and hypersensitivity. A positive history of bronds and the patient should be questioned to obtain a medical history with emphasison allergy and hypersensitivity. A positive history of bronds. should be questioned to obtain a medical history with emphass on allergy and hypersensitivity. A positive history of bronchial asthma or allergy (including food), a family history of allergy, or a previous reaction or hypersensitivity to a contrast agent may imply a greater than usual risk. Such a history may be more accurate than pre-testing in predicting the potential for reaction, although not necessarily the seventry or type of reaction, although not necessarily the seventry or their type does not arbitrarily contraindicate the use of a contrast agent when a diagnostic procedure is thought essential, but does call for caution. (See ADVERSE FRACTIONS.)

Prophylactic therapy including corticosteroids and anti-histamines should be considered for patients who present with a strong allergic history, a previous reaction to a contrast medium, or a positive pre-test since in these patients the incidence of reaction is two to three times that of the general

dence of reaction is two to three times that of the genera population. Adequate doses of corticosteroids should be started early enough prior to contrast medium injection to be effective and should continue through the time of injection and tor 24 hours after injection. Antihistamines should be adminis-tered within 30 minutes of the contrast medium injection.

tered within 30 minutes of the contrast medium injection. Recent reports indicate that such per-treatment does not prevent serious life-threatening reactions, but may reduce both their incidence and severity. A separate syringe should be used for these injections. General anesthesia may be indicated in the performance of some procedures in selected patients, however, a higher incidence of adverse reactions has been reported in these patients, and may be attributable to the inability of the patient to identify untoward symptoms or to the hypotensive effect of anesthesia which can prolong the circulation time and increase the duration of contact of the contrast agent. Anglography should be avoided whenever possible in patients with homocystimus because of the risk of inducing thrombosis and embolism.

PRECAUTIONS FOR SPECIFIC PROCEDURES

SPECIFIC PROCEDURES

Pediatric Angiocardiography: It is advisable to monitor for ECG and wilal signs changes throughout the procedure. When large individual doses are administered, sufficient time should be allowed for any observed changes to return for one are baseline prior to making the next injection. Caution should be used when making right heart rigidual results with pulmonary hypertension or incipient heart failure, since this may lead to increased right side pressures with subsequent bradycardia and systemic hypotension. Patients with pulmonary disease present additional risks. Caution is advised in cyanotic infants since apnea, pradycardia, other arrhythmiss and a tendency to acidosis are

bradycardia, other arrhythmias and a tendency to acidosis are more likely to occur.

Since intants are more likely to respond with convulsions

Since infants are more likely to respond with convulsions than are adults, the amount of total dosage is of particular importance. Repeated injections are hazardous in infants weighing less than 7 kg, particularly when these infants have pre-existing compromised right heart function or obliterated pulmonary vascular beds.

Selective Coronary Arteriography with or without left ventriculography: During the administration of large doses of HEXABRIX, continuous monitoring of vital signs is desirable. Caution is advised in the administration of large volumes to patients with incipient heart failure because of the possibility of aggravating the pre-existing condition. Hypotension should be corrected promptly since it may result in serious arrhythmias. Special care regarding dosage should be observed in patients with right ventricular failure, pulmonary hypertension, or stenotic pulmonary vascular beds because of hemodynamic changes which may occur after injection into

tension, or stenotic pulmonary vascular beds because of hemodynamic changes which may occur after injection into the right heart outflow tract.

Peripheral Arteriography. Moderate decreases in blood pressure occur frequently with intra-arterial (brachial) injections. This change is usually transient and requires no treatment, however, the blood pressure should be monitored for approximately ten minutes following injection.

Extreme caution during injection of the contrast agent is necessary to avoid extravastion and fluoroscopy is recommended. This is especially important in patients with severe arterial disease.

Cerebral Angiography Cerebral angiography should be performed with special caution in patients with advanced arteriosclerosis, severe hypertension, cardiac decompensation, senility, recent cerebral thrombosis or embolism, and migraine.

migraine.

Intra-Arterial Digital Subtraction Angiography: The risks associated with IA-DSA are those usually attendant with catheter procedures. Following the procedure, gentle pressure hemostasis is required, followed by observation and immobilization of the limb for several hours to prevent hemorrhage from the site of arterial puncture

Patient motion, including respiration and swallowing, can result in misregistration leading to image degradation and non-diagnostic studies

Intravenous Digital Subtraction Angiography: The risks associated with IV-DSA include those usually attendant with associated with IV-OSA include those usually attendant with translated solutions and include intransural injections, vessel dissection and tissue extravastion. The potential risk is reduced when small test injections of contrast medium are made under fluoroscopic observation to insure that the eatherler tips properly positioned and, in the case of peripheral placement, that the vein is of adequate size.

Patient motion, including respiration and swallowing, can result in misregistration leading to image degradation and non-diagnostic studies.

Peripheral Venography. Special care is required when venography is performed in patients with suspected thrombosis, phiebitis, severe ischemic disease, local infection or a totally obstructed venous system

Extreme caution during injection of contrast media is necessary to avoid extravasation and fluoroscopy is

recommended. This is especially important in patients with severe arterial or venous disease. Excretory Urography: Infants and small children should not have any fluid restrictions prior to excretory urography. (See WARNINGS and PRECAUTIONS concerning preparatery

dehydration.)
Contrast Enhancement in Body Computed Tomogram Patient cooperation is essential since patient motion, including respiration, can markedly affect image quality. The use of an intravascular contrast medium can obscure tumors in patients undergoing CT evaluation of the liver, resulting in a false nega-

tive diagnosis. Dynamic CT scanning is the procedure of choice for malignant tumor enhancement.

Arthrography. Strict aseptic technique is required to prevent the introduction of infection. Fluoroscopic control should be used to insure proper introduction of the needle into the synovial space and prevent extracapsular injection. Aspiration of excessive synoval fluid will reduce the pain on injection and prevent the dilution of the contrast agent. It is important that undue pressure not be exerted during the injection.

Hysterosalpingography. Caution should be exercised in patients suspected of having cervical or tubal carcinoma to avoid possible spread of the lesion by the procedure. Delayed onset of pain and fever (1-2 days) may be indicative of pelvic infection.

pelvic infection

pevic intection.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term animal studies have been performed to evaluate carcinogenic potential. However, animal studies suggest that this drug is not mutagenic and does not affect fertility in males

or females. Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at doses up to two times the maximum adult human dose and have revealed no evidence of impaired fertility or harm to the fetus due to HEXABRIX. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. **Nursing Motthers.** loxaglate salts are excreted unchanged in human milk. Because of the potential for adverse effects in nursing infants, bottle feedings should be substituted in our signal fractions.

nursing infants, bottle feedings should be substituted for breast feedings for 24 hours following the administration of this drug

Pediatric Use: Safety and effectiveness in children has be residual of Salety and effectiveness in clinical as seen established in pediatric angiocardiography and intravenous excretory urography. Data have not been submitted to support the safety and effectiveness of HEXABRIX in any other

(Precautions for specific procedures receive comment

ADVERSE REACTIONS

Adverse reactions to injectable contrast media fall into two categories: chemotoxic reactions and idiosyncratic reactions. Chemotoxic reactions result from the physiochemical

properties of the contrast media, the dose and the speed

properties of the contrast media, the dose and the spield of injection. All hemodynamic disturbances and injuries to organs or vessels perfused by the contrast medium are included in this category. Idiosyncratic reactions include all other reactions. They occur more frequently in patients 20 to 40 years ald kilosyncratic reactions may or may not be dependent on the dose injected. the speed of injection, the mode of injectionand the radiographic procedure. I diosyncratic reactions are subdivided into minor, intermediate and severe. The minor reactions are self-limited and of short duration; the severe reactions are life-threatening and treatment is urgent and mandatory.

mandatory

NOTE: Not all of the following adverse reactions have been reported with HEXABRIX. Because HEXABRIX is an iodinated intravascular contrast agent, all of the side effects and toxicity associated with agents of this class are theoretically possible, and this should be borne in mind when HEXABRIX is

administered. Severe, life-threatening anaphylactoid reactions, mostly of cardiovascular origin, have occurred following the administration of HEXABRIX as well as other iodine-containing confirst agents. Most deaths occur during injection or 5 to 10 minutes later, the main leature being cardiac arrest with cardiovasaular disease as the main aggravating factor. Isolated reports of hypotensive collapse and shock are found in the literature. Based upon clinical literature, reported deaths from the administration of conventional iodinated contrast agents range from 6.6 per 1 million (0.00066 percent) to 1 in 10.000 patients (0.01 percent). Repardiess of the contrast agent employed, the overall

10.000 patients (0.01 percent).
Regardless of the contrast agent employed, the overall estimated incidence of serious adverse reactions is higher with coronary arteriography than with other procedures.
Cardiac decompensation, serious arrhythmias, or imyo-

with Coronary arterlography unan ware over processors. Cardiac decompensation, serious arrhythmias, or myo-cardial ischemia or infarction may occur during corenary arteriography and left vehriculography.

The most frequent adverse reactions are nausea, wmitting, facial flush and a feeling of body warmth. These are usually of brief duration. In double-blind clinical trials, HEXABRIX:produced less discomfort upon injection (pain and heal) when compared to various other contrast agents. Other reactions include the following:

Hypersensitivity reactions: Dermal manifestations of urticaria with or without pruritus, erythema and maculopapular rash. Dry mouth. Sweating, Conjunctival symptoms: Facial, peripheral and angioneurotic edema. Symptoms related to the respiratory system include sneezing, assal stuffiness, coughing, choking, dyspnea, chest tightness and wheezing, which may be initial manifestations of more severe and infrequent reactions including asthmatic attack, larnyngospasm and bronchespasm with or without edema, pulmonary spasm and bronchospasm with or without edema, pulmonary edema, apnea and cyanosis. Rarely, these allergic-type

reactions can progress into anaphylaxis with loss of con sciousness, coma, severe cardiovascular disturbances and death

and death.

Cardiovascular reactions: Generalized vasodilation, flushing and venospasm. Occasionally thrombosis or, rarely, thrombophlebitis. Extremely rare cases of disseminated thrombophlebitis. Extremely rare cases of disseminated intravascular coagulation resulting in death have been reported. Severe cardiovascular responses include rare cases of hypotensive shock, coronary insufficiency, cardiac arrhythmia, librillation and arrest. These severe reactions are usually reversible with prompt and appropriate management; however, tatalities have occurred. Technique reactions: Extravasation with burning pain, hematomas, ecchymosis and tissue necrosis, vascular constriction due to injection rate, thrombosis and thrombonal-hebitis.

thrombophlebitis.

Neurological reactions: Spasm, convulsion cope, paresis, paralysis resulting from spinal cord injury and pathology associated with the syndrome of transverse myelitis visual field losses which are usually transient but may Other reactions: Headache, trembling, shaking, chills

Other reactions: Headache, trembling, shaking, chills without lever, hyperthermia and lightheadedness. Temporary renal shutdown or other nephropathy. Pediatric angiocardiography has been complicated by intramural injection with marked adverse effects on cardiac function.

During selective coronary arteriography with or without left ventriculography, patients may have clinically insignificant ECG changes. The following adverse effects have occurred in conjunction with the administration of iodinated intravascular contrast agents for this procedure: hypotension, shock, anginal pain, myocardial infarction, cardiac arrhythmias (bradycardia, ventricular tashycardia, ventricular fibrillation) and cardiac arrest. Fatalities have been reported. Com-

and cardiac arrest. Fatalities have been reported. Complications to the procedure include dissection of coronary artenes, dislogement of atheromatous plaques, perforation, hemorrhage and thrombosis. Following peripheral arteriography, hemorrhage and thrombosis have occurred at the puncture site of the percutaneous injection. Brachial plexus injury has been reported following axillary artery injection. The major causes of cerebral arteriographic adverse reactions appear to be repeated injections of the contrast material, administration of doses higher than those recommended, the presence of occulsive atherescienciou sexusical disease and the method and technique of injection. Adverse reactions are normally mild and transient. A feeling of warmth in the face and neck is frequently experienced, infrequently, a more severe burning discomfort is observed. Transient visual hallucinations have been reported. Serious neurological reactions that burning discomfort is observed. Transient visual hallucina-tions have been reported. Serious neurological reactions that have been associated with cerebral angiography and not listed under Adverse Reactions include stroke, amnesia and respira-tory difficulties. Visual field defects with anopsia and reversible neurological deficit lasting from 24 hours to 48 hours have been reported. Confusion. disorientation with hallucination, and absence of visitor is sometimes listing for one week have also been reported. Cardicvascular reactions that may occur with some frequency, are bradycardia and either an increase or decrease in systemic blood pressure. The blood pressure change is transient and usually requires no treatment. Arthrography may induce joint pain or discomfort which is Arthrography may induce joint pain or discomfort which is usually mild and transient but occasionally may be severe and persist for 24 to 48 hours following the procedure. Effusion requiring aspiration may occur in patients with rheumatoid arthritis. Fever and pain, cramping and tenderness of the abdomen have been reported following hysterosalpingography

OVERDOSAGE

Overdosages may cocur. The adverse effects of overdosage are life-threatening and affect mainly the pulmonary and cardiovascular systems. The symptoms may include cyanosis, bradycardia, acidosis, pulmonary hemorrhage, convulsions, coma and cardiac arrest. Treatment of an overdose is directed toward the support of all vital functions and prompt institution of symptomatic therapy. loxaglate salts are dialyzable

The intravenous LD₅₀ values of HEXABRIX (in grams of iodine/kilogram body weight) were 11.2 g/kg in mice, 8 g/kg in rats, >6.4 g/kg in rabbits and > 10.2 g/kg in degree.

DOSAGE AND ADMINISTRATION

Details on dosage are provided in the package insert. CON-SULT FULL PACKAGE INSERT BEFORE USE.

Rev. Nov. 1989

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Safety and Efficacy of In-Office Cardioversion for Treatment of Supraventricular Arrhythmias

Michael F. Lesser, MD

irect-current cardioversion has been an accepted technique for the correction of supraventricular arrhythmias nearly since its introduction by Lown et al in 1962.1 Although multiple reports documenting complications, and describing potential complications of this procedure have been reported,²⁻⁴ its overall safety has been well demonstrated both for emergent as well as elective intervention over the past 25 years.⁵ In fact, we now routinely treat patients for life-threatening arrhythmias as "outpatients" with the automatic implantable cardioverter-defibrillator. 6,7 Despite this, few, if any, published reports are available on the routine use of this in-office technique to correct common supraventricular arrhythmias such as atrial fibrillation and atrial flutter. Use of this technique has been reported in an outpatient setting in a hospital emergency room8 not only with excellent efficacy and safety, but also with rapid (2 hours) discharge and ambulation. This report describes our results of a routine procedure for countershock therapy applied to outpatients in a routine, in-office setting.

The Melbourne Cardiac Institute, a division of The Osler Medical Clinic, is a private practice cardiology group following approximately 10,000 patients. One examining room was converted to a "monitoring room" by adding a hospital bed and telemetry unit, which could transmit around the corner to the nursing station and general patient care area. The purpose of the room was to care for semiacute illnesses in our cardiac patients, in the hope of avoiding hospitalizations for significant, but routine (e.g., congestive heart failure) medical/cardiac problems. The room otherwise is set up as any other examining room, although a television and lounge chair were added for family members and to provide a relaxing atmosphere. After several years of admitting patients to the hospital for routine "outpatient" cardioversions, it was decided that similar efficacy and safety could be obtained at a significantly reduced cost by doing the procedure in the office. The additional benefits of saved physician and patient time, reduced anxiety for the patient by avoiding hospitalization, and the advantage of having a physician on site in the hours after the cardioversion, made this concept additionally attractive.

All patients with supraventricular arrhythmias, who were hemodynamically stable, were eligible for the study. No patient was excluded because of age, ventricular function or extent of medical therapy. All procedures

were done in the "monitoring room" as previously described. Telemetry monitoring with transmission to the nurses station (30 feet away) was available. Each patient underwent an identical protocol. If the patient was taking antiarrhythmic medications, therapy including digoxin was continued. The patient was instructed to avoid eating breakfast, and present to the office typically before 10 A.M. An electrolyte panel was recorded (run STAT in office), and a baseline electrocardiogram was obtained. All patients were given an anticoagulant regimen of warfarin (mean Protime 17.8) for a minimum of 2 weeks unless the documented duration of the arrhythmia was <48 hours or there was a specific contraindication to its use, in which case aspirin was given (to <10% of patients). Most patients also underwent echocardiography (available in office) before the procedure to exclude the possibility of gross, undiagnosed intracardiac thrombi. Although we recognized the limited sensitivity of this procedure, this was done additionally to minimize risk because of the limited documentation of similar approaches in published reports.

Informed consent was obtained and the patient was prepared with anteroposterior paddle locations using electrode pads. The local emergency medical service was notified that a cardioversion was going to be performed. An intravenous line was begun (at the time blood was drawn) and was used for the administration of between 3 and 30 mg of intravenous diazepam or midazolam. Usually the patients became unconscious within 30 to 120 seconds. When they no longer responded to voice, synchronized cardioversion with 160 to 360 J was attempted. Up to 3 shocks were applied in some cases before restoration of sinus rhythm. All shocks were done with continuous monitoring available both through the cardioverter device as well as remote monitoring. A "STAT-KIT" (Banyan Co.) complete with all necessary "crash cart" drugs and devices was available in the room at all times.

Typically, the patients were awake and alert within 2 hours of the procedure, some at 30 minutes and completely amnestic of the experience. No patient required emergency transport or hospitalization after the procedure. The patients were aged 35 to 94 years (mean 65). Forty-seven (68%) were men, 22 (32%) women; 54 (78%) had atrial fibrillation, 15 (22%) atrial flutter. Underlying diseases were mixed coronary/valvular (45%), coronary artery disease (25%), hypertension (18%), alcoholic cardiomyopathy (7%) and miscellaneous (5%). Ejection fractions ranged from 16 to 74% (mean 54), with 11 patients (16%) having ejection fractions <40% and 7 patients (10%) ejection fractions <25%. Left atrial size ranged from 2.2 to 5.5 cm (mean 3.8).

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An average energy of 214 J was required, reflecting our usual starting energy of 220 J. This was adjusted downward on several occasions either because of the patients' rhythm (atrial flutter), advanced age or small size. Fifteen patients (34%) had multiple cardioversions (separate days). Diazepam anesthesia was administered as the initial 6 procedures (range 12 to 25 mg, mean 17); however, midazolam was given to the remaining 63 (range 3 to 30 mg, mean 7).

Primary success was obtained in 64 of 69 procedures (93%), with 85% converting on the first shock. Twentyfive (57%) remain in sinus rhythm after a follow up of 1 to 41 months (mean 18). Twenty-three (92%) continue to take digoxin and 18 (72%) concomitant antiarrhythmic

therapy.

Arrhythmias occurred after 15 cardioversions (22%). These typically were short-lived runs of supraventricular or ventricular extrasystoles in the immediate postconversion (5 minutes) period. Additional pharmacologic intervention for tachy- or bradyarrhythmias was necessary only in 1 patient. Specifically, this consisted of intravenous atropine and subsequently low-dose (0.1 mg) epinephrine to correct a persistent marked sinus bradycardia with slow junctional escape, which nevertheless was not accompanied by hypotension.

Three late events did occur, thought to be partly related to the cardioversion procedure itself. One 85year-old woman developed acute pulmonary edema, requiring hospitalization 8 hours after going home. This was associated with a significant hypertensive episode, and similar events had occurred previously. In addition to significant hypertension and moderate systolic dysfunction, the patient had prominent left ventricular hypertrophy and moderate renal insufficiency, and was presumed to have significant "diastolic" failure as well. A 70-year-old man had an embolism in the leg 24 hours after cardioversion for atrial fibrillation, despite therapy with warfarin (Protime 18.8). He was hospitalized and successfully treated with intravenous thrombolytic therapy. A 68-year-old man died 48 hours after cardioversion of unknown causes. This same patient had undergone 2 previous cardioversions, in the same outpatient environment, without incident. A phone discussion with his widow revealed episodes of chest pain the evening of his death and it was believed that the most likely cause was acute myocardial infarction, especially since he had coronary artery disease documented by cardiac catheterization. An autopsy was not performed. Had his cardioversion been done in a hospital, he would presumably have been discharged the following morning and thus would have died the second night after hospital dis-

This report details that cardioversion can be performed routinely and safely in an outpatient setting. Additional precautions were taken because of age, underlying heart disease, and also limited reporting of similar approaches. Nevertheless, in no instance was a procedure

rescheduled because of electrolyte abnormalities, no patient required emergency transport to the hospital, and no notable late (≥20 minutes after the procedure) arrhythmias were picked up by the telemetry monitoring system.

The implications of this study are significant. In these times of declining health care dollars, significant savings can be obtained by performing this procedure as an outpatient. In our area, the typical charge for an inhospital "outpatient" cardioversion is about \$900. Add an overnight stay, and it can rapidly go as high as \$1,300 to \$1,400. The same procedure can be performed in the office for \$250 to \$400. If we assume a similar potential frequency of potential outpatient cardioversions among the general population of cardiologists of 1 per month, and assume an average cost savings of \$250 per cardioversion (very conservative) and extrapolate this to the approximately 3,000 cardiologists nationwide we arrive at a cost savings of \$9,000,000 a year. I believe this to be a very conservative figure and twice this amount may be closer to the real figure. The advantage of all this is that savings are accomplished with an improvement in the delivery of care without any loss of efficacy or safety. Patients are actually much more receptive to an outpatient cardioversion, rather than being hospitalized for the same procedure. Most associate the hospital with significant illness or dangerous procedures and thus become more apprehensive about the whole process. Doing the same procedure in the outpatient environment is actually somewhat reassuring. In addition, because we took "all comers," including those advanced in age, as well as with significant left ventricular dysfunction, we have demonstrated efficacy and safety in a rather nonselect patient population. Because many had significant underlying heart disease, we have proven safety and efficacy in a patient population from which we would expect more than the average number of adverse outcomes.

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Effects of Amlodipine on Blood Pressure, Heart Rate, Catecholamines, **Lipids and Responses to Adrenergic Stimulus**

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anagement of systemic hypertension with calcium antagonists is gaining increasing acceptance. Antihypertensive therapy with these agents, however, is limited by frequent adverse effects and need for frequent daily doses. Amlodipine is a new dihydropyridine derivative currently undergoing evaluation for therapy of hypertension. Although qualitatively similar to nifedipine, amlodipine has a longer duration of action and may be useful as a single daily dose.² This study evaluated effects of different doses of amlodipine given once daily to patients with mild to moderate hypertension. Its effects on adrenergic response to isometric exercise³ and plasma levels of catecholamines and lipids were also evaluated.

Ambulatory patients with a diastolic blood pressure (BP) between 95 and 114 mm Hg during 2 consecutive clinic visits were eligible for the trial. Patients with severe angina, heart block, severe or labile hypertension, failure of any major organ system, recent myocardial infarction or cerebrovascular accident were excluded.

The study was divided into 2 segments each of which lasted 4 weeks. Segment I, a single-blind placebo period, was designed to confirm diagnosis and stability of hypertension and familiarize patients with experimental procedures.

In segment II (treatment phase) each patient received either placebo or amlodipine 2.5, 5 or 10 mg/day in a double-blind fashion. Patients were instructed to take their medication once daily at 8:00 AM except on clinic appointments days. On these days medication was taken after completion of experimental procedures.

During each clinic visit BP and heart rate (HR) were measured in the supine position after 5 minutes of rest and again after 1 minute of quiet standing. After another 5 minutes of rest, BP and HR were again measured before and after 1 minute of sustained isometric handgrip.

At the end of segments I and II, laboratory tests to assess hematologic, renal or hepatic dysfunction were performed. Also, fasting plasma lipid profiles and levels of catecholamines were obtained at the same time. Subsequently, each patient was admitted to the Clinical Research Center where supine and erect BP and HR were measured hourly for 12 hours and again 24 hours later. During each clinic visit patients were questioned about

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adverse drug reactions and tablet counts were performed to assess compliance.

BP and HR during isometric handgrip and at the end of segments I and II in supine and erect positions were compared using Student's t test for paired data. Oneway repeat-measures analysis of variance was used to evaluate BP and HR changes over 24 hours. Subsequent pairwise comparisons were made with Student's t test for paired data employing Bonferroni's correction. A p value ≤0.05 was considered significant.

Sixteen patients entered and completed both segments of the trial. All were men aged 43 to 74 years (mean \pm standard error of the mean 61 \pm 2) with mean duration of hypertension of 12 ± 3 years. Baseline characteristics of these patients were similar (Table I).

Placebo therapy had little effect on BP and HR. Monotherapy with amlodipine, however, reduced BP without affecting HR (Figure 1). No significant differences were detected between different doses of amlodipine with respect to antihypertensive effect (Table I). Consequently, all data from patients receiving all doses of amlodipine were combined for all subsequent analyses.

TABLE I Summary of Patients **Amlodipine** Placebo 2.5 mg 5.0 mg 10.0 mg (n = 4)(n = 4)(n = 4)(n = 4)Baseline supine 162/101 153/99 166/102 163/101 blood pressure ±8/±2 $\pm 7/\pm 1$ ±7/±2 ±5/±2 (mm Hg) Baseline erect 164/103 149/101 168/101 153/103 ±7/±3 ±6/±1 ±13/±2 $\pm 5/\pm 3$ blood pressure (mm Hg) 66±1 61 ± 4 63 ± 4 57 ± 2 Age (yrs) 181 ± 7 218 ± 20 Weight (lbs) 176 ± 15 203 ± 10 Race 4W/0B 3W/1B 2W/2B 1W/3B **Smokers** 135 ± 60 63 ± 2 96 ± 69 257 ± 95 Duration of hypertension (mos) Erect Supine SBP DBP SBP DBP Blood Pressure Changes (mm Hg) -2 +2 +5 0 Placebo Amlodipine (2.5 mg) -11* -5 -13*-11*

-5

-10*

-10*

-17*

-9*

-11*

-6

-11*

Amlodipine (5.0 mg)

Amlodipine (10.0 mg)

Changes in supine BP and HR over 24 hours after 4 weeks of therapy with placebo or amlodipine are shown in Figure 2. BP over 24 hours was reduced by amlodipine (p <0.02) by all doses evaluated, whereas HR was minimally affected.

Sustained isometric handgrip was associated with increases in BP and HR in placebo-treated patients. BP was lower in patients taking amlodipine, but it increased by the same magnitude as in placebo-treated patients (difference not significant). HR also increased similarly in patients taking placebo or amlodipine (Figure 3).

Patients taking placebo complained of leg pain (n = 1), headache (n = 2), ankle edema (n = 1), anxiety (n = 1) and chest wall pain (n = 1). Leg pain and headache (1) patient each) were also reported during amlodipine therapy. No clinically significant changes in clinical laboratory values were observed during placebo or amlodipine therapies. All observed adverse effects were mild and none required discontinuation of any patient from the trial.

Plasma concentrations of total cholesterol, triglycerides, and high-density lipoprotein cholesterol were unchanged during therapy with amlodipine, whereas low-density lipoprotein cholesterol decreased significantly (165 ± 17 vs 133 ± 12 mg/dl, p = 0.01). Plasma concentrations of norepinephrine increased (410 ± 31 vs 554 ± 55 ng/ml, p = 0.02), whereas those of epinephrine and dopamine were unaffected.

In this study, amlodipine effectively reduced BP without affecting HR. Furthermore, administration of single daily doses ranging from 2.5 to 10.0 mg resulted in reduction of BP for the entire 24-hour dosing period. BP reduction with amlodipine, 2.5 mg/day, was indistinguishable from doses of either 5.0 or 10.0 mg/day. Effectiveness of lower doses of amlodipine in this study may be related to the higher mean age of patients in this study compared with ages of patients in previous studies (61 vs 50 years). Calcium antagonists have been more effective as antihypertensive agents at lower doses in the elderly than in younger hypertensive counterparts. 5.6

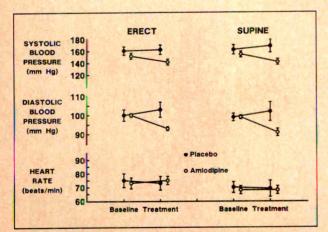


FIGURE 1. Comparative effects of placebo and amlodipine on erect and supine blood pressures and heart rates. Heart rate was unaffected by amlodipine, whereas blood pressure was significantly reduced. Data are presented as mean \pm standard error of the mean.

The observation that use of amlodipine preserves the daily pattern of BP and HR fluctuations is novel and probably important. Similar effects on BP and HR have not been observed in patients treated with nadolol or atenolol but have been reported in association with verapamil and nifedipine. Whether preservation of such fluctuations in BP and HR is beneficial with use of amlodipine is unclear. However, such preservation is probably physiologic.⁷

Although other calcium antagonists have been shown to exert α -adrenergic blocking effects,³ we observed no significant effect of amlodipine on BP response to isometric handgrip, a potent α -adrenergic stimulus. Absence of α -adrenergic blockade may relate to the fact that adverse effects such as orthostasis, nasal stuffiness, or both, were not observed in our patients.

We observed a slight but significant decline in plasma concentrations of low-density lipoproteins, whereas total cholesterol and triglyceride levels were unaffected in amlodipine-treated patients. Currently, there is emphasis on potential adverse effects of some antihypertensive agents on plasma lipid profiles. Minimal effects on plasma lipids exerted by amlodipine in this study are in marked contrast to adverse effects of other antihypertensive agents,

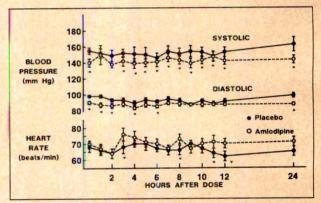


FIGURE 2. Variation in supine blood pressure and heart rate during placebo or amlodipine (all doses) therapy. Data are presented as mean \pm standard error of the mean. $*=p \le 0.05$ refers to within group (baseline-final) comparison.

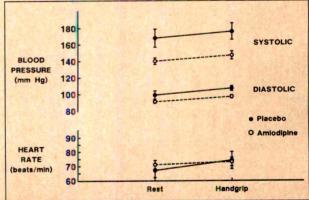


FIGURE 3. Mean changes in blood pressure and heart rate in response to sustained handgrip exercise. Blood pressure and heart rate increased similarly during therapy with placebo and amlodipine. Data are presented as mean \pm standard error of the mean.

such as β blockers and diuretics on plasma lipids. Similarly, amlodipine-induced changes in plasma catecholamines were also minor. Plasma norepinephrine levels increased slightly, whereas epinephrine and dopamine were not affected. Notably, even though concentrations of norepinephrine were elevated, HR was not increased. This observation suggests that amlodipine does not suppress some responses to sympathetic stimulation.

In summary, amlodipine reliably reduces BP for a full 24-hour dosing period without causing reflex tachycardia. Such BP reduction is achieved while α -adrenergic response and physiologic fluctuations in BP and HR were preserved. Adverse effects were infrequent and mild.

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Effect of Mitral Regurgitation on the Left Ventricular Outflow Pressure Gradient in Obstructive Hypertrophic Cardiomyopathy

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ynamic left ventricular (LV) outflow obstruction was first described in a patient with concentric LV hypertrophy by Brock¹ in 1957. Three years later, Braunwald et al² reported 12 patients with idiopathic hypertrophic subaortic stenosis; 11 of 12 had mitral regurgitation (MR) demonstrated either at operation or by the reflux of dye into the left atrium. Using catheterization, it has been demonstrated that interventions that decrease or increase outflow obstruction may decrease or increase MR.^{3,4} However, the latter study found no statistically significant correlation between the degree of MR and the LV outflow gradient. To investigate this relation noninvasively, we reviewed Doppler echocardiographic studies in a large series of patients with hypertrophic cardiomyopathy (HC).

Between July 1987 and November 1989, 116 patients with HC had M-mode, 2-dimensional, pulsed Doppler, continuous wave and color-flow echocardiography. These 116 studies were retrospectively reviewed and 7 patients (6%) were excluded: 4 because of concomitant valvular aortic stenosis, and 3 because the studies were not technically adequate. The remaining 109 patients comprised the study group. There were 58 men and 51 women; their ages ranged from 38 to 91 (mean 69 ± 11) years. Patients were included only if they had both asymmetric septal hypertrophy and mitral systolic anterior motion.

All echocardiograms were done on commercially available equipment. The LV outflow gradient was determined by continuous wave Doppler, with care taken to orient the direction of the transducer so as to obtain a 0° angle with the direction of flow from the apex. Pulsed

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Doppler was used to localize the area of obstruction to the outflow tract. The outflow velocity was easily recognized by its characteristic late-peaking configuration. The degree of MR was determined from the color-flow studies.5 This was done in a semiguantitative fashion by evaluating the jet of MR visually in multiple orthogonal planes and assessing the area of the jet as well as the relation of the jet area to the area of the left atrium. Because the grading of MR was done individually over the study period by the 5 cardiologists in the laboratory before this retrospective review, the grading was done blindly with respect to the purpose of this study.

Chi-square analysis was used to compare the degree of MR with the degree of LV outflow gradient. Patients with gradients <36 mm Hg (flow velocities <3.0 meters/ second [m/s]) had mild obstruction. Patients with gradients from 36 to 63 mm Hg (flow velocities 3.0 to <4.0 m/ s) had moderate obstruction. Patients with gradients ≥64 mm Hg (flow velocities ≥4.0) had severe obstruction. This was followed by residual analysis. Analysis of variance was used to analyze the mean LV outflow gradients among groups with differing degrees of MR. Because group variances are unequal, as detected by Levine's test for homogeneity of variance, the Welch and the Brown-Forsythe tests were used to analyze variance. Because only 4 patients had severe MR, they were ex-

TABLE I Degree of	i wiitrai Reg	urgitation		
	None	Mild	Moderate	Severe
LVOT velocity		1 - 13-6	以"如事"和	
<3m/s(%)	21 (31)	39 (57)	8(12)	0(0)
3-3.9 m/s(%)	5 (26)	7 (37)	5 (26)	2(11)
≥4m/s(%)	3(14)	7 (32)	10 (45)	2(9)

cluded from the latter 2 tests to minimize unequal group sizes. The mean outflow gradient in these 4 patients was higher than that of patients in any of the other groups.

A p value <0.05 was considered significant. In the residual analysis, the familywise error rate was also kept at 0.05.

Eighty of 109 patients with HC had MR (73.4%). Mild MR was present in 53 (48.6%), moderate MR in 23

(21.1%) and severe MR in 4 (3.7%).

Sixty-eight of 109 patients had LV outflow velocities <3.0 m/s (no or mild gradients). Nineteen patients had outflow velocities from 3.0 to 3.9 m/s (moderate gradients). The remaining 22 patients had resting LV outflow velocities ≥4.0 m/s (severe gradients). The highest resting gradient was 150 mm Hg (range 0 to 150, mean 30 ± 36 mm Hg). Forty-three patients (39%) had no resting outflow gradients. Thirty-five of those with no resting gradients were provoked with the Valsalva maneuver (8 patients), amyl nitrite inhalation (25 patients) or both (2 patients). Twenty-seven of the 35 patients who were provoked developed outflow gradients with provocation (77%). These provocable gradients ranged from 16 to 164 mm Hg (mean 51 mm Hg). MR was assessed at rest only, and not with provocation.

The incidence of varying degrees of MR in patients with varying degrees of outflow obstruction is summarized in Table I. Of the 68 patients with no or mild gradients, 21 had no MR (31%), 39 had mild MR (57%), 8 had moderate MR (12%) and none had severe MR. Of the 19 patients with moderate gradients, 5 had no MR (26%), 7 had mild MR (37%), 5 had moderate MR (26%) and 2 had severe MR (11%). The remaining 22 patients had severe resting outflow gradients. Three of these had no MR (14%), 7 had mild MR (32%), 10 had moderate MR (45%) and 2 had severe MR (9%).

Since mild MR on Doppler has been demonstrated in many normals, 6-9 we divided our study patients into 2 groups—those with no or mild MR and those with moderate or severe MR (who were considered to have significant MR). Of the 68 patients with no or mild resting outflow gradients, 60 had no or mild MR (88%) and only 8 had significant MR (12%). Of the 19 patients with moderate resting gradients, 12 had no or mild MR (63%) and 7 had significant MR (37%). Of the remaining 22 patients with severe resting gradients, 10 had no or mild MR (45%) and 12 had significant MR (55%).

Chi-square analysis revealed that the MR and the outflow gradients are associated (chi-square = 18.1, p = 0.0001). To interpret the chi-square results, residual analysis was done. To keep the familywise error rate at the 0.05 level, the Bonferroni method for correction was used. The p value for the residual analysis of each cell had to be less than 0.008 (0.05/6 cells). This corresponds to a z value of 2.41, which was exceeded by the 4 cells corresponding to the groups with no or mild gradients and high gradients. Thus, the chance of having a high outflow gradient with no or mild MR is significantly less than in patients with significant MR.

The mean outflow gradient in patients with no, mild, and moderate MR was 20, 23, and 51 mm Hg, respectively. Analysis of variance showed that this difference was statistically significant (Welch test p = 0.0141; Brown-Forsythe test p = 0.0046). The mean outflow gradient in the 4 patients with severe MR was 70 ± 38

It was recognized very early that the MR that occurred in patients with HC was occurring in association with normal mitral leaflets, as seen in the operating room, and the mechanism of MR was thought to be a distortion of the mitral apparatus by the hypertrophied septum.2 When systolic anterior motion was noted on LV contrast angiography, MR could be seen occurring under the mitral leaflets. It was postulated that coaptation of the leaflets was prevented by this abnormal motion. 10 MR was shown to be mainly midsystolic in 20 of 22 patients with HC, and that it came and went with the obstruction during followup or pharmacologic interventions. 11 In 28 patients studied by pulsed Doppler echocardiography, all of the 14 patients with systolic anterior motion had MR, whereas only half of the 14 without systolic anterior motion had MR. 12 This group did not comment on the severity of MR, only on its presence. Other authors have found that the administration of angiotensin resulted in the relief of the outflow gradient as well as the abolition of MR.4 In 1 study, angiotensin resulted in a decrease in the outflow gradient as well as the MR in 11 of 15 patients and no change in the MR despite a drop in outflow gradient in the other 4 patients; however, this group found no statistical correlation between the outflow gradient and the degree of MR before the administration of angiotensin.13 A recent study did show a correlation between the degree of MR and the outflow gradient at rest, 14 but only 16 patients were evaluated. Another group studied 10 patients with color Doppler echocardiography, and found that the degree of MR was not related to the severity of systolic anterior motion. 15

In view of these conflicting findings, we sought to evaluate a large group with HC using Doppler echocardiography to assess the pathophysiologic changes in these 109 patients. Our findings show that there is a convincing direct relation between the degree of outflow obstruction and the degree of MR. In fact, moderate MR was seen in only 12% of those with little or no outflow obstruction, and severe MR was not present at all in this group (0% of 68 patients). In contrast, moderate or severe MR was present in 55% of those with severe resting outflow gradients. The results were highly statistically significant.

MR may play an important clinical role in further elevating the left atrial pressure, which is already high in these patients with diastolic LV dysfunction. Fortunately, the same treatment may reduce both the obstruction and the MR, as they are interrelated. We have recently shown that the degree of MR decreases in patients with severe aortic stenosis when their valvular gradients are reduced with aortic valve replacement. 16 A prospective study before and after medical therapy for HC would help to elucidate the relation further in these patients.

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Combined Obstructive Hypertrophic Cardiomyopathy and Stenotic Congenitally Bicuspid Aortic Valve

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pypertrophic cardiomyopathy (HC) is a congenital heart disease. Persons with 1 type of congenital heart disease are more prone to a second congenital heart condition than are persons without any congenital cardiac condition. The frequency of the congenitally bicuspid aortic valve in the general population is believed to be about 1%. Therefore, it might be expected to be present in an occasional patient with a more uncommon condition, such as HC. The present report describes findings in 4 patients with coexisting HC and a congenitally bicuspid aortic valve.

The records of the Surgery Branch, National Heart, Lung, and Blood Institute, were searched for all patients who had a cardiac operation for HC and who had coexisting aortic valve disease. From 1960 to 1990 a total of 525 patients with HC underwent ventricular septotomy and partial septectomy (hereafter referred to as myotomy and myectomy) and 29 (5%) of them had coexisting aortic valve disease: pure aortic regurgitation in 20 patients and aortic valve stenosis with or without regurgitation in 9 patients. Of the latter 9 patients, 5 had tricuspid aortic valves, and 4 had bicuspid aortic valves. This report focuses on the 4 patients with combined HC and stenotic congenitally bicuspid aortic valves.

Pertinent findings in the 4 patients are summarized in Table I. All 4 patients were in New York Heart Association Functional class III or IV. Patients 1 and 2 had other family members with HC. Grade 3/6 systolic precordial murmurs, loudest along the left sternal border, were audible in all 4 patients, and the murmur was made louder by standing or by the Valsalva maneuver. Patients 1, 3 and 4 had a second systolic murmur that

radiated to the neck, suggestive of valvular aortic stenosis. By echocardiogram the thickness of the ventricular septum was considerably greater (ratio >1.6) than that of the left ventricular free wall, and systolic anterior motion of the anterior mitral leaflet was present in all 4 patients. The peak systolic pressure gradient between the left ventricle and ascending aorta was >70 mm Hg in all 4 patients (Figure 1). At operation, all 4 patients had calcified, stenotic, congenitally bicuspid aortic valves (Figure 2). A typical mural endocardial plaque in apposition to the anterior mitral leaflet was present in all 4 patients. The ventricular septum by palpation was severely thickened and typical of that found in HC associated with a normal aortic valve. The portions of excised ventricular septum histologically had myofibril disorganization consistent with HC. All 4 patients had a lessening of their symptoms of cardiac dysfunction late postoperatively.

Coexisting HC and valvular aortic stenosis have been reported in at least 30 patients since 1960,²⁻⁴ but usually the only evidence of HC was a ventricular septum thicker than the left ventricular free wall. Although asymmetric septal hypertrophy is usually present in HC, it also occurs in about 10% of patients with valvular aortic stenosis, and in about 10% of patients with systemic hypertension.^{5,6} Thus, to diagnose HC in the presence of valvular aortic stenosis, findings other than a disproportionately thickened ventricular septum are necessary, and such was the case in the 4 patients described here.

The congenitally bicuspid aortic valve appears to occur with the same frequency in patients with obstructive HC as in the general population (each about 1%). At least 2 patients with HC and a congenitally bicuspid stenotic aortic valve have been reported by others. One,³ a 52-year-old man, had a 73-mm Hg peak systolic left ventricular outflow pressure gradient, a ventricular septum con-

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	Follow- Up After	AVR	Cl (yrs) FC	16.5 1	7.2 2	2.6 1	7.3 2	;; § highest	York Heart sg = peak wn.
			C	2.2 16.5	2.8	2.5	1	pass grafting	class (New yectomy; p: — = unkno
	Six Months Postoperative Catheterization	LV-AA psg [§]	Rest Provoked (mm Hg)	90	20	30	1	**Left ventricle to ascending aorta pullback pressure measurements demonstrated <25 mm Hg aortic valvular component to the gradient. **Inchookable gradient to 125 mm Hg with isoproterenol. ** concomitant coronary artery bypass grafting. ** highest	provide gradient measured during Vassava materies. Internation of mussion of software of mussion of software provided and a second material managed and material mussion of software of the second software of
	ive Cathe	LV-A	1	72 10	30 22	30 25	90 -	int coronai	female; FC A = myoto = present:
	ostoperat	AAP	(mm Hg)	150/5 140/72 10	0 142/80	150/10 125/80	130/80	concomita	= male; F = male; MN r septum; +
	Months Pc	LVP	Type (Size) (1–4) s/d(mm Hg)	150/5	160/10	150/1	1	proterenol;	x (liters/min pressure; M = ventricular
\$	Six	esis	FC FC (1–4	(21) 1	(19) 2	(27) 1	(27) 2	lg with isop	ardiac inde) It ventricle p implex; VS =
tic Valves		- AV Prosthesis	Type (§	BS (2	BS [‡] (1	SJM# (2	H	125 mm H	ation; CI = c
iotic Aor		AV	Weight (g)	4.7	1.4	7.2	1	gradient to	a = calcifica cular free wa entricular pr
spid Sten	ata	Amount VS LVOT AV	Mural Ca Wei Plaque (0-4) (g)	4+	2+	4+	3+	provokable	ork Shiley; C = left ventric al; VPC = ve
ally Bicus	Morphologic Data	unt VS LV	ed Mi	+	+	+	+	gradient; †	int; BS = Bic
Congenit	Morp	Amo	Excised AM (g)	4.7	1.1	1.4	1.0	nent to the	replaceme left ventrio
thy and ((mm) S	45 +	46 +	45 +	48 +	ular compor	aortic valve aortic valve atrium; LV =
omyopat		Echo Data	psg AR + VPC VS LVFW LA Exc (mm Hg) Cl (0-4) Response (mm) (mm) (mm) SAM (g)	12	13	12	10	<25 mm Hg aortic valvular component to the gradient; † p	soproterence alve; AVR = y; LA = left a /end-diasto
ic Cardi		E	SV Sonse (m	22	21	21	25	<25 mm Hg	Nusion of the Nu
pertroph			AR + VPC (0-4) Respor	+	+	+ +	+ +	nonstrated -	rigitation; A rophic card et; s/d = pe
oined Hy		. 1	B) CI (6	2.4 2+	2.3 0	2.6 1	1.8 2+	ements den	ation of arm = aortic regi +C = hypert r mitral leaf
ith Com	ation	AAP LV-AA	psg (mm)	5 142*	123/62 115*	5 95*.1	145/60 75	ure measur	essure; AR = srosthesis; He anterio
TABLE I Findings in Four Patients with Combined Hypertrophic Cardiomyopathy and Congenitally Bicuspid Stenotic Aortic Valves	'W		mm Hg)	235/12 93/56 142*	123/6	350		Ilback press	provokable gradient measured during valsava manever, implation to anyn intre or AA = ascending actor; AAP = ascending aortic pressure; AR = aortic regurgitation; A Association; IF = family instory; H = Hancock bioprosthesis; HC = hypertrophic card systolic gradient; SAM = systolic anterior motion of the anterior mitral leaflet; s/d = pr
n Four Pa	perative C	LVP	of FC HC (1–4) s/d(mmHg)	235/12	238/10	195/5	220/9	ng aorta pui	P = ascendi story; H = H stolic anteric
indings ir	Preo	H	of FC HC (1-4)	+ 4	+ 3	0 3	0 4	to ascendi	nent measuring aorta; AAI = family his
BLEIF		ДОР		57 /F	57/M	58/M	64/M 0 4	eft ventricle	A = ascendir ciation); FH olic gradient
4			F. 8	-	2	3	4		Asso Asso syste

siderably thicker than the left ventricular free wall, and systolic anterior motion of the anterior mitral leaflet; he underwent both aortic valve replacement and myotomy and myectomy. The second,4 a 48-year-old woman with a family history of HC, had a 120-mm Hg peak systolic pressure gradient between the left ventricle and aorta, and a ventricular septum considerably thicker than the left ventricular free wall; she underwent aortic valve replacement only.

The operatively excised valves in our 4 patients actually appeared considerably more stenotic than was the degree of valvular stenosis found at preoperative cardiac catheterization. In our 4 patients, however, valvular aortic stenosis was anticipated because of the presence of an additional precordial murmur, calcific deposits in the aortic valve on chest x-ray, and aortic regurgitation.

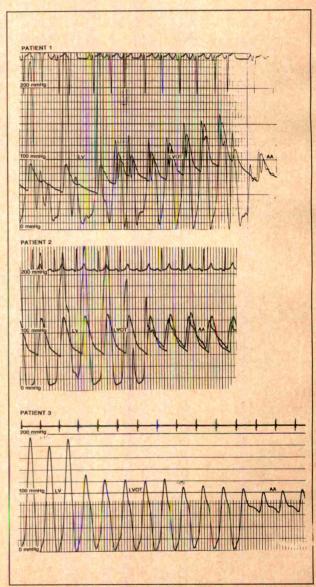


FIGURE 1. Left ventricle to ascending aorta pullback pressure tracings. The pressure gradient was primarily subvalvular with a <25 mm Hg valvular component in patients 1 to 3. AA = ascending aorta; LV = left ventricle; LVOT = left ventricular outflow tract.

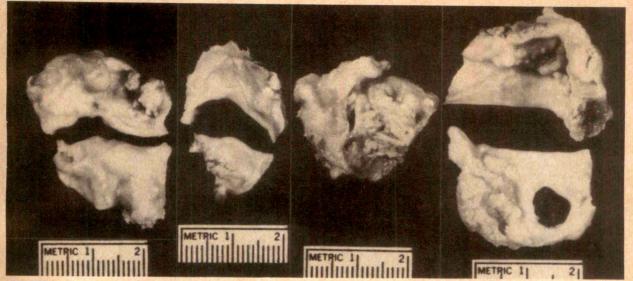


FIGURE 2. Excised stenotic bicuspid aortic valves from the 4 patients are shown from left to right. Valve no. 4 had a large perforation that was blocked by an area of calcium from the opposite leaflet.

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Experience with the Gianturco-Roehm Bird's Nest Vena Cava Filter

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tects patients with lower extremity deep venous thrombosis from pulmonary embolism. It is the procedure of choice for patients who either cannot be anticoagulated, or have had recurrent pulmonary embolism despite anticoagulation. Extensive experience with the Greenfield vena cava filter (Medi-tech Inc., Watertown, Massachusetts) has shown long-term caval patency rates of >95%, and rates of recurrent pulmonary embolism of <5%. However, a malposition rate as high as 14%, ^{2,3} premature filter release, ⁴ perforation of the inferior vena cava and associated structures, ⁵ and femoral vein thrombosis at the site of insertion of remain potential problems.

The Gianturco-Roehm Bird's Nest Filter (Cook Inc., Bloomington, Indiana), approved for clinical use by the Food and Drug Administration in 1989, was designed to

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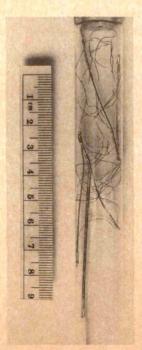


FIGURE 1. The Gianturco-Roehm Bird's Nest vena cava filter.



FIGURE 2. The fine wire mesh filter occupies a 6- to 7-cm length of inferior vena cava.

overcome some of the disadvantages of the Greenfield filter. Designed for percutaneous introduction through the jugular, subclavian and femoral approaches, it consists of 2 rigid, V-shaped struts, between which are attached four 25-cm-long, 0.18-mm diameter stainless steel wires (Figure 1). Properly positioned, the fine wire mesh filter occupies a 6- to 7-cm length of inferior vena cava (Figure 2).

From December 1989 to March 1990, 5 patients, 3 men and 2 women aged 32 to 81 years, underwent Bird's Nest filter placement by the femoral approach at our facility. All had malignancies with pulmonary embolism or deep venous thrombosis, and contraindications to or failure of anticoagulation.

The Bird's Nest filter delivery system consists of a 12Fr sheath designed for insertion over a 0.038-inch guidewire, and an 11Fr filter-carrying catheter.7 The catheter contains the filter, an attached pusher wire for filter advancement and release, and a sidearm allowing injection of contrast distally to facilitate filter positioning. After obtaining venous access percutaneously, vena cavography is performed to assess the presence of thrombus, size of the inferior vena cava and renal vein locations. The distal ends of the sheath and filter-carrying catheter are positioned just below the renal veins, usually located near the L1-L2 vertebral interspace. While holding the pusher wire stable, the catheter/ sheath assembly is withdrawn to expose the distal filter strut while maintaining its junction point just inside the catheter. Gentle advancement of the catheter/sheath assembly 1 to 3 mm secures the strut and its anchoring hooks in the wall of the inferior vena cava. The catheter/

TABLE I Characteristics and Complications of Greenfield and Bird's Nest Filters7,10

	Greenfield Filter	Bird's Nest Filter
Length (mm)	41	70
Diameter (mm)	30	54
Carrier size (Fr)	24	11
Maximal caval diameter (mm)	30	40
Recurrent pulmonary embolism (%)	5	3
Caval patency (%)	95	97
Femoral vein thrombosis (%)	<15	unreported
Migration (%)	uncommon	0*
Vascular perforation	uncommon	Rare

Food and Drug Administration approved second-generation device with rigid

sheath assembly is then withdrawn an additional 1 to 3 cm over the stationary pusher wire to release the distal strut from the catheter. This maneuver permits passage of the filter wires by further advancement of the pusher wire, and provides room for filter formation within the inferior vena cava. The filter catheter/sheath assembly is then advanced so that the junction point of the proximal strut, which still remains in the catheter, overlaps the junction point of the distal strut by 1 to 2 cm, thus packing the loops of wire in the inferior vena cava. While maintaining forward pressure on the pusher wire, the catheter/sheath assembly is withdrawn to permit the proximal strut to exit the catheter. Gentle to-and-fro motion on the pusher wire secures this strut and its anchoring hooks in the inferior vena cava. The pusher wire is then rotated counterclockwise 10 to 15 turns to disengage it from the filter, after which the pusher wire and empty filter catheter are removed. The sheath is then repositioned, and vena cavography repeated to confirm filter placement.

Successful infrarenal filter placement was achieved in all 5 patients by the femoral approach. Although generally a simple technique, passage of the 12Fr sheath and filter catheter was difficult in 1 case in which the inferior vena cava was distorted by retroperitoneal tumor. The entire procedure, from vena cavography to completion, usually required 20 to 30 minutes. No acute complications, such as groin or retroperitoneal hematoma, were noted. Anticoagulation was used when possible after the procedure. During follow-up of 1 to 4 months, there was no clinical evidence of local femoral vein thrombosis, vena caval thrombosis, recurrent pulmonary embolism or filter migration.

The commercially available Greenfield vena cava filter offers caval patency in greater than 95% of cases with a low rate of recurrent pulmonary embolism (Table I). Although initially designed for placement by venous cutdown, percutaneous methods of delivery have been developed and are widely used.8 Despite this and other improvements, technical problems such as angulated and misplaced filters, which may fail to protect the patient from pulmonary embolism, 2,3 and local complications such as femoral vein thrombosis, which may be related to trauma from the 24Fr filter carrier device,6 still occasionally occur.

The Gianturco-Roehm Bird's Nest Filter, designed for percutaneous insertion only, is effective with incidences of clinically suspected recurrent pulmonary embolism of 2.7% and inferior vena cava occlusion of 2.9% after 6 months in 440 patients receiving the initial first and second generations of this device.7 Potential advantages when compared to the Greenfield filter include a negligible incidence of clinically recognized femoral vein thrombosis when delivered percutaneously from this site. As the Bird's Nest filter is a cluster of wires, meticulous alignment within the inferior vena cava, as with the Greenfield filter,9 is unnecessary. Additionally, after a design change incorporating rigid filter struts, there have been no reported cases of Bird's Nest filter migration. However, as migration may be related to poor seating in an oversized vena cava, caution is recommended with this device when inferior vena cava diameter exceeds 40 mm.

Randomized clinical trials of the Bird's Nest, Greenfield, and other investigational vena cava filters are lacking. Until such data are available, the choice of device should be based on the operator's experience, the clinical situation and analysis of the current published reports.¹⁰

Our experience with the Bird's Nest filter has been favorable, and it has proved useful in the management of a difficult and fortunately uncommon clinical problem.

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Frequencies of Reactions to Iohexol Versus Ioxaglate

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adiographic contrast material causes a variety of complications and reactions. In an attempt to minimize these events, alternative contrast agents have been developed, which either reduce the osmolality per iodine molecule, or reduce the number of charged particles in solution, or both.1-8 Reduction of charged particles in solution makes some of the newer agents less chemotoxic than older ionic agents. 5,6,9 It has been demonstrated that the nonionic contrast agents have fewer hemodynamic and electrophysiologic effects than their ionic counterparts. Myocardial contractility and vascular motor tone are less affected by the newer agents, as are heart rate and myocardial depolarization and repolarization. 1,4,6,7 It has been shown that nonionic agents such as iohexol and iopamidol cause fewer allergic, "anaphylactoid" reactions than standard ionic agents. 8,9 Little data compare the incidence of reactions with a low osmolar nonionic agent such as iohexol with the low osmolar ionic dimer, ioxaglate. The purpose of this study was to examine the occurrence of such events in a group of patients treated at the same institution with 1 or the other of these agents over the same time period under similar circumstances.

This study was performed as a Department of Pharmacy focus investigation at St. Luke's Hospital of Kansas City, Missouri. The hospital records of 534 consecu-

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tive patients who were studied in the cardiac catheterization laboratory in November and December 1989 were reviewed for the occurrence of adverse or allergic reactions. Patients underwent coronary angiograms or percutaneous transluminal coronary angioplasty, or both, and received either iohexol or ioxaglate for radiographic contrast (Table I). In 5 cases, the type of contrast was not specified, resulting in a study group of 529. None of these 5 patients had an adverse reaction. Cardiac catheterization and angioplasty were performed using standard technique. Each cardiologist at our center uses only 1 of the newer agents for all his cases, based on which he feels is safest. As there is no significant cost difference for these agents at our hospital, each cardiologist always uses his preferred substance for all patients, both high and low risk. No routine premedication for prophylaxis of allergic reactions was given unless a history of contrast allergy was obtained, in which case prednisone and diphenhydramine were administered before the procedure. Most patients received either no sedative premedication for their procedure or small intravenous or oral dosages of a benzodiazepine such as diazepam or midazolam. All patients undergoing angioplasty received 10,000 U of heparin intravenously at the beginning of the procedure, augmented by additional boluses of 5,000 U at hourly intervals or as dictated by activated clotting times performed in the catheterization laboratory. Heparin was not routinely used for angiography without angioplasty. Plastic syringes were used in all cases. Ad-

TABLE I Patient Groups				
	lohexol	loxaglate	Total	
Pts.	205	324	529	
Procedure				
Angiography (%)	135 (66)	142 (44)	277 (52)‡	
Angioplasty (%)	70 (34) p < 0.001	182 (56)	252 (48)§	
Gender				
Male (%)	138 (67)	243 (75)	381 (72)	
Female (%)	67 (33)	81 (25)	148 (28)	
Age (yrs)	63±11	62±11	63 ± 11	
Previous contrast or	11 (5)	11 (3)	22 (4)	
iodine allergy (%)				
Adverse reactions				
Allergic only*				
Hives	4	20	22	
Sneezing	0	5	5	
Itching	1	4	5	
Other [†]	1	5	6	
Total allergic	6(3)p<0.05	27 (8)	33 (6)	
reactions (%)				
Nausea/vomiting (%)	0 (0) p < 0.001	9 (3)	9(2)	
Total adverse	6(3)p<0.005	35 (11)	41 (8)	

reactions (%)

* Some patients had more than 1 type of allergic reaction.

† Other reactions included lip edema, shortness of breath, seizure, profound flushing, throat tightness.

18 total and 15 allergic reactions occurred in this group (6.5 and 5.4%, respec-

tively). § 23 total and 16 allergic reactions occurred in this group (9.1 and 6.3% of this

group, respectively).

Difference not significant in reaction incidence between angiography vs angio-

verse reactions were reported by the catheterization laboratory technical staff, confirmed by the cardiologist and recorded by the technical staff. As the technical staff continuously rotates with all physicians, they served as a control to minimize reporting bias by individual physicians. Neither the cardiologist nor the catheterization laboratory technicians were aware that this study was to be performed. Hospital charts were reviewed by members of the Department of Pharmacy for recorded adverse and allergic reactions and other pertinent data. No pharmaceutical company or concern was aware of, participated in, or supported this study.

Values are expressed as mean ± 1 standard deviation. Group characteristics were compared by chisquare analysis with Yates' correction. A p value < 0.05 was considered significant for differences between patient groups.

Table I compares the incidence of reactions in the groups treated with iohexol versus ioxaglate. There was a highly significant difference in the occurrence of reactions to these 2 types of contrast material, with ioxaglate showing a significantly higher rate of reported events, whether total adverse reactions or allergic responses alone were considered. There was no significant difference in the incidence of previously documented contrast or iodine allergy between the groups (iohexol [n = 11]5%, ioxaglate [n = 11] 3%). There was no significant difference in the overall incidence of allergic or total reactions between patients who had coronary angiography alone versus angioplasty. The incidence of reactions during angiography alone was higher with ioxaglate (10%) than with iohexol (3%), as was the incidence of reactions during angioplasty (11 and 3%, respectively). Allergic reactions were usually treated with intravenous diphenhydramine and occasionally with intravenous steroids. No deaths occurred as a consequence of the reactions noted previously. No thromboembolic event, significant arrhythmia or pulmonary edema occurred in any patient. The clinical characteristics of the patient groups were similar, other than the type of procedure done (Table I). However, the type of procedure (angiography versus angioplasty) did not influence the incidence of reactions, as noted previously.

Those adverse reactions attendant to high osmolality are reduced by agents such as ioxaglate, which have lower osmolality than ionic contrast. However, ioxaglate is an ionic dimer consisting of charged particles in solution that still maintains many of the chemotoxic properties of standard, older ionic contrast agents. Our study emphasizes that, as a possible consequence of its reduced chemotoxic effect, a nonionic agent such as iohexol causes a highly significant reduction in adverse and allergic phenomena when compared to ioxaglate.

The main limitation of widespread use of the newer nonionic contrast agents is their higher cost when compared to older ionic materials. 10 However, a cost advantage does not hold true for ioxaglate, as it is also quite expensive. Many laboratories routinely use 1 of the newer low osmolar agents because of their increased safety and better patient tolerance. When all factors other than cost consideration are taken into account, the use of the newer, low osmolar agents is strongly preferred. Our study indicates that when agents of similar cost such as iohexol and ioxaglate are to be used, the nonionic agent iohexol is significantly safer than the ionic dimer ioxaglate. Although none of the patients in this study died as a consequence of a contrast-related adverse reaction, it would appear prudent to use an agent with a significantly safer profile.

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Safety and Usefulness of Transesophageal Echocardiography in Persons Aged ≥70 Years

Elizabeth O. Ofili, MD, MPH, and Michael W. Rich, MD, with the technical assistance of Peggy Brown and Jean Lewis

lthough transthoracic echocardiography remains the cornerstone of diagnostic cardiac ultrasound, satisfactory images cannot be obtained in up to 20% of patients. It may be particularly difficult to acquire high quality images in patients on mechanical ventilators, after major thoracic surgery, and in the elderly. In addition. transthoracic echocardiography is of limited value in assessing prosthetic valves, atrial masses and aortic dissection.^{1,2} In contrast, transesophageal echocardiography (TEE) provides a superior acoustic window and overcomes many of the limitations of the transthoracic approach. Although several studies have described the safety and utility of TEE,1-7 the role of this technique in evaluating elderly patients needs clarification. This report describes our initial experience with TEE in the awake setting in 35 consecutive patients aged ≥70 years.

From February 1989 to February 1990, 35 patients aged ≥70 years underwent nonoperative TEE at this institution. Mean age was 79 years (range 70 to 86), 14 patients (40%) were men, and 54% were in New York Heart Association functional class III or IV. Eight patients (23%) had recently undergone cardiac surgery, and 10 patients (31%) were on mechanical ventilators. All patients had transthoracic echocardiograms before

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LA LV
RA
RV

FIGURE 1. Transesophageal modified 4-chamber view in systole showing ruptured tip of papillary muscle (arrow) in the left atrium (LA). LV = left ventricle; RA = right atrium; RV = right ventricle.

TEE. In 19 patients (54%) the transthoracic study was technically suboptimal for diagnosis; in the remaining patients, TEE was performed for further clarification. TEE was performed at bedside in 19 patients and in the endoscopy suite in 16 patients.

Informed consent was obtained and patients were fasting for 6 hours before the procedure. Local anesthetic spray (cetacaine) was used to anesthetize the oropharynx in all patients; 30% of cases required no additional sedation. In the remaining patients, intravenous midazolam, 0.5 to 5.0 mg, provided adequate sedation. TEE was performed according to previously described techniques^{2,4,6} using the Aloka SSD 870 (Corometrics Medical Systems, Inc., Wallingford, Connecticut) or the Acuson 128 (Acuson Corporation, Mountainview, California). No examination lasted >15 minutes and the procedure was well tolerated by all patients. One patient developed mild hypotension after intravenous sedation. This responded promptly to fluid administration. Another patient developed transient respiratory depression, which resolved after supplemental oxygen was initiated.

The indications for TEE were: hemodynamic instability (n = 15), suspected prosthetic valve dysfunction (n = 5), bacterial endocarditis (n = 4), suspected left atrial mass (n = 4), cerebrovascular accident (n = 3), aortic dissection (n = 2), atrial septal defect (n = 1), and diagnostically inadequate transthoracic study (n = 1). In 24 patients (69%), TEE provided new or conclusive

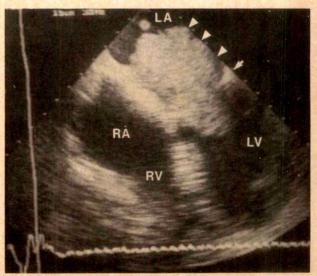


FIGURE 2. Transesophageal modified 4-chamber view in diastole demonstrating gelatinous tumor mass (arrowheads) attached to the atrial septum and protruding through the mitral valve (arrow). LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

findings that allowed rapid and effective patient management without the need for additional invasive procedures. In 4 patients, the results of TEE led to major changes in patient management and expeditious surgical intervention. One patient underwent successful coronary angioplasty after an acute inferior wall myocardial infarction, but later developed refractory hypotension. An emergent transthoracic echocardiogram was nondiagnostic, but TEE demonstrated a ruptured papillary muscle (Figure 1) and the patient underwent successful mitral valve replacement. Two other patients also underwent successful mitral valve replacement after TEE showed severe mitral regurgitation due to flail leaflets. A fourth patient presented with transient ischemic attacks. Transthoracic echocardiogram showed a poorly defined mass in the left atrium and ventricle. A prior history of malignant melanoma suggested the possibility of metastic disease. TEE clearly demonstrated a gelatinous mass attached to the atrial septum consistent with a myxoma (Figure 2), and the tumor was successfully excised. In another patient, TEE revealed an unsuspected large periprosthetic leak from a bioprosthetic mitral valve; unfortunately, this patient died while preparations for surgery were being made.

In 19 patients, the clinical impact of TEE was less dramatic than in the patients just described, but the procedure still provided important information directly affecting subsequent patient management. In 6 patients, unnecessary medications, including antibiotic and anticoagulant therapy, were discontinued, whereas in another 6, a medication change based on TEE findings led to clinical improvement. Finally, in 7 additional patients TEE provided definitive diagnoses that led to the avoidance of further tests or procedures, including cardiac

catheterization.

The role of TEE in clinical decision-making continues to evolve. High quality images can be safely obtained in both the intraoperative and awake settings. 1-6 Despite being a modestly invasive technique, our data show that TEE is well tolerated by elderly patients, even when they are critically ill. These findings are consistent with studies in younger patients1 and less ill subjects.5 Hypotension and respiratory depression may occur after intravenous sedation, but in our early experience these problems respond readily to conventional therapy. Importantly, we have found that most elderly patients require minimal sedation: In up to one-third of patients, local anesthesia is sufficient, whereas in the remaining patients, 0.5 to 1 mg of intravenous midazolom is often adequate.

Although this study is limited by its small sample size, our data suggest that TEE is particularly useful in specific subsets of elderly patients. Critically ill subjects on

mechanical ventilators or after recent cardiothoracic surgery can be rapidly and effectively evaluated by this technique.^{2,5} These patients may develop sudden hemodynamic deterioration requiring rapid diagnosis and treatment. The superior acoustic window provided by the esophageal approach, coupled with the absence of lung and chest wall interference, may make TEE the imaging procedure of choice in these patients. Similarly, in patients with mechanical complications after acute myocardial infarction or with suspected severe mitral regurgitation, the surface echocardiogram may be inadequate for accurate diagnosis,3 whereas TEE is frequently conclu-

TEE is also valuable in the differential diagnosis of suspected intracardiac masses. Artifacts caused by reflection of ultrasound waves from calcified structures such as the mitral anulus may mimic mass lesions in elderly patients undergoing transthoracic echocardiograms. In our study, TEE provided definitive information in 9 of 10 patients in whom the transthoracic study was nondiagnostic with regard to a possible cardiac mass, thrombus or vegetation.

A final situation in which TEE is particularly useful is in the assessment of prosthetic valves.^{2,6} In our study, 5 patients with suspected prosthetic valve dysfunction were evaluated and in each case TEE provided clear visualization of the valve and yielded definitive diagnostic information which, in 1 patient (Figure 1), led to prompt referral for surgery.

These preliminary data indicate that TEE can be performed safely in elderly patients, and that it frequently provides important diagnostic information that has a significant impact on clinical management.

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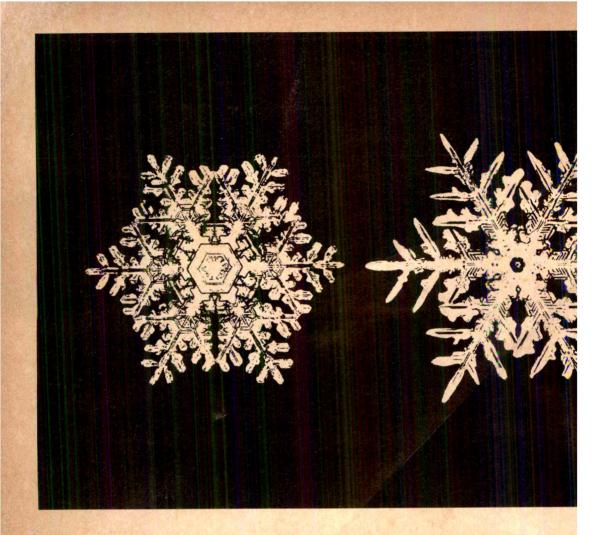
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Before prescribing, please see full prescribing information. A Brief Summary follows.

CONTRAINDICATIONS. 1. Hepatic or severe renal dysfunction, including primary biliary cirrhosi

Preexisting gallbladder disease (See WARNINGS)

 A. Hypersensitivity to gemfibrozil.

WARNINGS. 1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated sub iects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed choleithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization (WHO), 5000 subjects without known conducted by the World Health Organization (WHO). onary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant, 29%, higher total mortality in the clofibrate treated than in a comparable placebo-treated control group. The excess mortality was due to a 33% increase in noncardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

During the Helsinki Heart Study and in the 1½ year follow-up period since the trial was completed, mortality from any cause was 59 (2.9%) in the Lopid group and 55 (2.7%) in the placebo group. Mortality from any cause during the double-blind portion of the study was 44 deaths in the Lopid group and 43 in the placebo group. Because of the more limited size of the Helsinki Heart Study, this result is not statisticallysignificantly different from the 29% excess mortality seen in the clothorate group in the separate WHO study. Noncoronary heart disease related mortality showed a 58% greater trend in the Lopid group (43 vs 27 patients in the placebo group, p=0.056)

In the Helsinki Heart Study, the incidence of total malignancies discovered during the trial and in the 1½ years since the trial was completed was 39 in the Lopid group and 29 in the placebo group (difference not statistically significant). This includes 5 basal cell carcinomas in the Lopid group and none in the placebo group (p=0.06; historical data predicted an expected 4.7 cases in the placebo group). GI malignancies and deaths

from malignancies were not statistically different between Lopid and placebo sub-groups. Follow-up of the Helsinki Heart Study participants will provide further information on cause-specific mortality and cancer morbidity.

 A gallstone prevalence substudy of 450
Helsinki Heart Study participants showed a trend toward a greater prevalence of gall-stones during the study within the Lopid treatment group (7.5% vs 4.9% for the place bo group, a 55% excess for the gemfibrozil group). A trend toward a greater incidence of gallbladder surgery was observed for the Lopid group (17 vs 11 subjects, a 54% ex-cess). This result did not differ statistically

from the increased incidence of cholecystectomy observed in the WHO study in the group treated with clofibrate. Both clofibrate and gemfibrozil may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected, gallbladder

studies are indicated. Lopid therapy should be discontinued if gallstones are found 3. Since a reduction of mortality from coronary artery disease has not been demonstrated and because liver and interstitial cell testicular tumors were increased in rats, Lopid should be administered only to those patients described in the INDICATIONS AND USAGE section. If a significant serum lipid response is not obtained, Lopid should

be discontinued.

4. Concomitant Anticoagulants – Caution should be exercised when anticoagulants are given in conjunction with Lopid. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined

that the prothrombin level has stabilized.

5. Concomitant therapy with Lopid and Mevacor® (lovastatin) has been associated with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria leading in a high proportion of cases to acute renal failure. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy rhabdomyolysis, and acute renal failure (See Drug Interactions). The use of fibrates alone, including Lopid, may occasionally be associated with myositis. Patients receiving Lopid and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myositis, including serum creatine kinase level determination. If myositis is suspected or diagnosed, Lopid therapy should be withdrawn.

Cataracts – Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of male rats treated with gemfibrozil at 10 times the human dose.

PRECAUTIONS. 1. Initial Therapy — Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal. Before instituting Lopid therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities.

2. Continued Therapy - Periodic determination of serum lipids should be obtained.

and the drug withdrawn if lipid response is inadequate after 3 months of therapy.

3. **Drug Interactions**—(A) **Lovastatin:** Rhabdomyolysis has occurred with combined gemfibrozil and lovastatin therapy. It may be seen as early as 3 weeks after initiation of combined therapy or after several months. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhab-domyolysis, and acute renal failure. There is no assurance that periodic monitoring of

creatine kinase will prevent the occurrence of severe myopathy and kidney damage (B) Anticoagulants: CAUTION SHOULD BE EXERCISED WHEN ANTICOAGU LANTS ARE GIVEN IN CONJUNCTION WITH LOPID. THE DOSAGE OF THE ANTI-COAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED

A. Carcinogenesis, Mutagenesis, Impairment of Fertility—Long-term studies have been conducted in rats and mice at one and ten times the human dose. The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant (p=0.1). In high dose female rats, there was a significant increase in the combined incidence of benign, and malignant liver applicance. In male and female might be true not statistically significant increase in the combined incidence of benign, and malignant liver neoplasms. In male and female mice, there were no statistically significant differences

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from controls in the incidence of liver tumors, but the doses tested were lower than those shown to be carcinogenic with other fibrates

Male rats had a dose-related and statistically significant increase of benign Leydig cell tumors at 1 and 10 times the human dose.

Electron microscopy studies have demonstrated a florid hepatic peroxisome prolifera-tion following Lopid administration to the male rat. An adequate study to test for perox-isome proliferation has not been done in humans but changes in peroxisome morphology have been observed. Peroxisome proliferation has been shown to occur in humans with either of two other drugs of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Administration of approximately three or ten times the human dose to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmit-

ted to the offspring.

5. Pregnancy Category B – Reproduction studies have been performed in the rat at doses 3 and 9 times the human dose, and in the rabbit at 2 and 6.7 times the human dose. These studies have revealed no evidence of impaired fert.lity in females or harm to the fetus due to Lopid. Minor fetotoxicity was manifested by reduced birth rates observed at the high dose levels. No significant malformations were found among almost 400 off-spring from 36 litters of rats and 100 fetuses from 22 litters of rabbits.

There are no studies in pregnant women. In view of the fact that Lopid is tumorigenic in

male and female rats, the use of Lopid in pregnancy should be reserved for those patients where the benefit clearly outweighs the possible risk to the patient or fetus.

6. Nursing Mothers — Because of the potential for tumorigenicity shown for gem-

fibrozil in rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

7. **Hematologic Changes – M**ild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of Lopid therapy. However, these levels stabilize during long-term administration. Rarely, severe anemia, leukopenia, thrombocytopenia, and bone marrow hypoplasia have been reported. Therefore, periodic blood counts are recommended during the first 12 months of Lopid administration.

8. Liver Function – Abnormal liver function tests have been observed occasionally during Lopid administration, including eleva-

tions of AST (SGOT), ALT (SGPT), LDH, bili rubin, and alkaline phosphatase. These are usually reversible when Lopid is discontinued. Therefore periodic liver function studies are recommended and Lopid therapy should be terminated if abnormalities persist.

9. **Use in Children** – Safety and efficacy in children have not been established. ADVERSE REACTIONS. In the double-blind controlled phase of the Helsinki Heart Study, 2046 patients received Lopid for up to 5 years. In that study, the following adverse reactions were statistically more frequent in subjects in the Lopid group (placebo incidence in paren-

(23.8%); dyspepsia, 19.6% (11.9%); abdominal pain, 9.8% (5.6%); acute appendicitis (histologically confirmed in most cases where data are available), 1.2% (0.6%); atrial fibrillation, 0.7% (0.1%).

Adverse events reported by more than 1% of subjects, but without a significant difference between groups (placebo incidence in parentheses) were: diarrhea, 7.2% (6.5%); fatigue, 3.8% (3.5%); nausea/vomiting, 2.5% (2.1%); eczema, 1.9% (1.2%); rash, 1.7% (1.3%); vertigo, 1.5% (1.3%); constipation, 1.4% (1.3%); headache, 1.2% (1.1%). Gallbladder surgery was performed in 0.9% of Lopid and 0.5% of placebo subjects, a 64% excess, which is not statistically different from the excess of gallbladder surgery observed in the clofibrate compared to the placebo group of the WHO study.

Nervous system and special senses adverse reactions were more common in the Lopid group. These included hypesthesia, paresthesias, and taste perversion. Other adverse reactions that were more common among Lopid treatment group subjects but where a causal relationship was not established include cataracts, peripheral vascular disease, and intracerebral hemorrhage

From other studies it seems probable that Lopid is causally related to the occurrence of musculoskeletal symptoms (See WARNINGS), and to abnormal liver function tests and hematologic changes (See PRECAUTIONS).

Reports of viral and bacterial infections (common cold, cough, urinary tract infections) were more common in gemfibrozil-treated patients in other controlled clinical trials of 805 patients.

Additional adverse reactions that have been reported for gemfibrozil are listed below

by system. These are categorized according to whether a causal relationship to treatment with Lopid is probable or not established:

CAUSAL RELATIONSHIP PROBABLE: Gastrointestinal: cholestatic jaundice; Central Nervous System: dizziness, somnolence, paresthesia, peripheral neuritis, decreased libido, depression, headache; Eye: blurred vision; Genitourinary: impotence; Musculoskeletal: myopathy, myasthenia, myalgia, painful extremities, arthralgia, synovitis, rhabdomyolysis (see WARNINGS and Drug Interactions under PRECAUTIONS); Clinical Laboratory: increased creatine phosphokinase, increased billirubin, increased liver transaminases (AST [SGOT], ALT [SGPT]), increased alkaline phosphatase; Hematopoietic: anemia, leukopenia, bone marrow hypoplasia, eosinophilia; Immunologic: angioedema, laryngeal edema, urticaria; Integumentary: exfoliative dermatitis rash dermatitis pruritus

CAUSAL RELATIONSHIP NOT ESTABLISHED: General: weight loss; Cardiac: extrasystoles; Gastrointestinal: pancreatitis, hepatoma, colitis; Central Nervous System: confusion, convulsions, syncope; Eye: retinal edema; Genitourinary: decreased male fertility, Clinical Laboratory: positive antinuclear antibody; Hematopoietic: thrombocytopenia; Immunologic: anaphylaxis, Lupus-like syndrome, vasculitis; Integumentary: alopecia DOSAGE AND ADMINISTRATION. The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening mea MANAGEMENT OF OVERDOSE. While there has been no reported case of over-dosage, symptomatic supportive measures should be taken should it occur.

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*Defined as a combination of definite coronary death and/or definite myocardial infarction.

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